

REScribing INFORMATION

LIPOBAY® 400 Microgram Tablets

Summary of Product Characteristics (prescribing) **Composition and Form:** Each tablet contains 400 micrograms of cerivastatin sodium. Each box contains 28 tablets. Lipobay® 400 Microgram Tablets contain 381.7mcg cerivastatin in the form of 400mcg cerivastatin sodium.

Therapeutic indications: Primary hypercholesterolaemia (Types IIA + IIB): The treatment of hypercholesterolaemia in patients who have not responded adequately to an appropriate diet. **Posology and Administration:** Exclude secondary causes of hypercholesterolaemia prior to therapy. Use standard cholesterol-lowering diet. Efficacy may be enhanced in combination with a bile-acid sequestrant (e.g. colestyramine).

Adults: Take once a day in the evening, with or without food. Start at 400mcg and titrate by 100mcg depending on response at four week intervals. Maximum dose of 400mcg. **Elderly:** Treatment should be initiated at the lower end of the dosage range. **Moderate to severe renal impairment:** Start at 100mcg and titrate with Maximum dose of 200mcg once-daily.

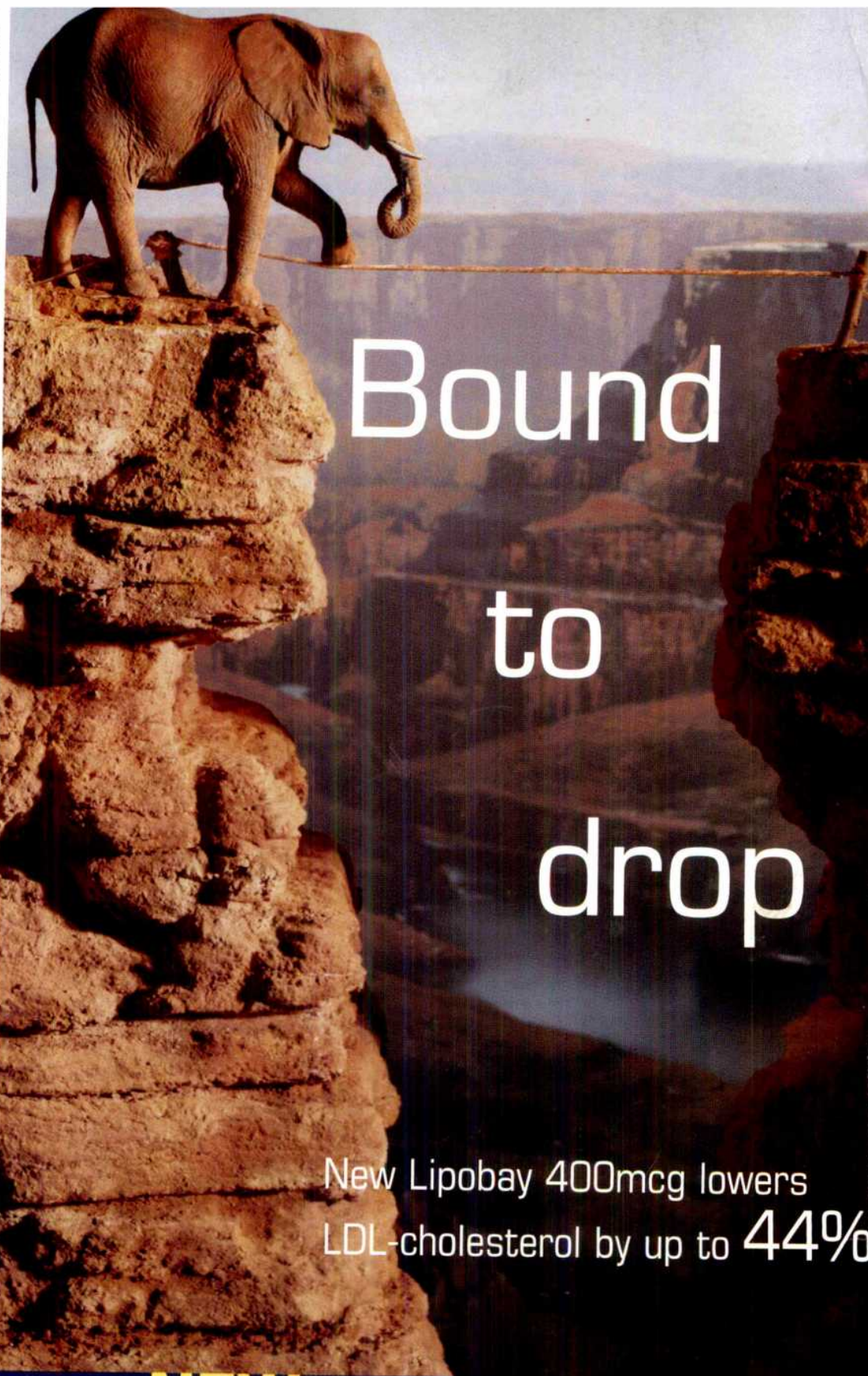
Children: Not recommended. **Contraindications:** Hypersensitivity; myopathy, muscle impairment or unexplained, persistent elevations in serum transaminases; pregnancy or lactation. Women of childbearing potential should use non-oral contraceptive methods. **Warnings:** **Liver function:** Increases in liver enzymes and, very rarely, cases of mostly minor and asymptomatic have occurred. Liver function tests are indicated. Discontinue therapy if increases in AST >3xULN. Caution in patients with history of heavy alcohol ingestion or liver disease. **Muscle:** Sporadic CPK elevations, usually clinically significant, have been reported. Rarely, myopathy, associated with elevations of CPK (>10xULN) and/or use of myalgias, muscle tenderness or weakness, has been reported. Patients report these symptoms, especially if accompanied by malaise or fever. Discontinue if markedly elevated CPK levels occur, or if myopathy is diagnosed or suspected. Risk of myopathy increases on concomitant administration with cyclosporin, fibric acid derivatives, erythromycin, miconazole and nicotinic acid. Cases of rhabdomyolysis (some with acute renal failure) have been reported in patients receiving lipobay in combination with gemfibrozil and, very rarely, on gemfibrozil monotherapy. Withhold Lipobay® temporarily from patients experiencing an intercurrent condition pre-disposing to myopathy or renal failure secondary to rhabdomyolysis. **Ophthalmological:** New cataracts and nuclear opacities have been reported, although, a causal relationship with Lipobay® has not been established.

Concomitant use: **Drugs known not to interact with cerivastatin:** Warfarin, digoxin, nifedipine, mibefradil, omeprazole, cimetidine, antacids. **Drugs that interact with cerivastatin:** Erythromycin, itraconazole, cyclosporin, gemfibrozil and bile acid sequestrants. Rifampicin or phenytoin effects are unknown. **Undesirable effects:** Abdominal pain, allergic reaction, dizziness, ischaemic colitis, angiodema, arthralgia, asthenia, constipation, diarrhoea, dyspepsia, eye disorders, flatulence, headache, hepatitis, increased CPK, insomnia, leg and arm pain, myalgia, myasthenia, myositis, nausea, paresthesia, rash, rhabdomyolysis and possibly mild transaminase (ALT/AST) elevations.

Legal category: POM. **Package size and basic NHS costs:** Calendar containing 28 tablets; Lipobay® 400 Microgram Tablets £17.35. **Marketing authorisation number:** PL 00010/0249. **Date of Preparation:** November 1999. For further information refer to Summary of Product Characteristics or contact: Bayer plc, Pharmaceutical Division, Bayer House, Berkshire, RG14 1JA Tel: (01635) 4000. © Bayer plc January 2000. ® Registered trademark of Bayer AG, Germany. Bayer, Baypharm and Lipobay are trademarks of Bayer AG.

Bayer

Reference
Lancet. Curr Med Res Opin 1999;15(3):228-



Bound to drop

New Lipobay 400mcg lowers
LDL-cholesterol by up to 44%

NEW LIPOBAY® 400
CERIVASTATIN

C6-H06364-47-P25312

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The Journal is specially related to the Association of Surgeons of Great Britain and Ireland, the Surgical Research Society, the Vascular Surgical Society of Great Britain and Ireland, the British Association of Endocrine Surgeons, EuroSurgery, the Surgical Infection Society (Europe), the European Society of Surgical Research and the Association of Surgeons of the Netherlands

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INDICATIONS

Tazocin is a broad spectrum penicillin for the treatment of bacterial infections caused by Gram-negative bacteria. Lower respiratory infections, urinary tract infections, otitis media, skin infections, septicæmia and polymicrobial infections, skin and lower respiratory tract infections, patients with host defences and in combination with an aminoglycoside in adult and paediatric patients with neutropenia.

Contraindications: Intravenous use only. Elderly/children over 12. Usually every 8 hours (range from 2.25-4.5g every 3 hours dependent on the severity of neutropenia 4.5g every 6 hours in combination with an aminoglycoside). 12 years and under: Only recommended for children with neutropenia as for adults with neutropenia weighing < 50kg when 90mg/kg every 8 hours, in combination with an aminoglycoside, is recommended. Renal impairment: Dosing reduction may be necessary, please consult data sheet.

Indications: Hypersensitivity to penicillins, cephalosporins or β -lactamase inhibitors.

Warnings: Discontinue if anaphylactic or allergic reaction occurs.

Side effects: Periodic assessment of hepatic and haematological functions advised. Discontinue if bleeding tendencies occur. Resistant bacteria may cause superinfection. Convulsions occur with higher than recommended doses. Possibility of hypokalaemia in patients with low potassium or on diuretics. Evaluate patients for gonorrhoea prior to treatment for gonorrhoea. Use during pregnancy or lactation: If benefits outweighs risk. **Side effects:** Most frequent: gastro-intestinal disturbances; various skin reactions including rashes, erythema, pruritus and urticaria; allergic reactions, superinfection, phlebitis, thrombophlebitis, inflammation at site of injection frequent: muscle pain or weakness, dizziness, dry mouth, stomatitis, oedema, tiredness and rarely penicillin, interstitial nephritis, neurological changes, increases in urea and rarely renal function test values have been reported. **Overdose:** Penicillin may be reduced by dialysis.

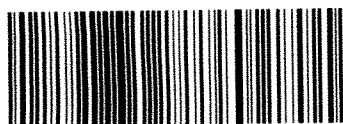
Contraindications: Tazocin 2.25g: Vials containing piperacillin 2g (as piperacillin) and tazobactam 250mg (as sodium). Tazocin 4.5g: Vials containing piperacillin 4g (as piperacillin) and tazobactam 500mg (as sodium). **Basic NHS Price:** strength: single vial £13.16, single 10 pack £14.48; 2.25g strength single vial £7.24, PL nos: 4.5g strength PL 00254; 2.25g strength PL 0095/0252; 4.5g vials 37/68/2; 4.5g combination 37/68/3; 2.25g vial 37/68/1. **Legal category:** POM. Further information is available on request from: Wyeth Laboratories, Huntercombe Lane South, Uxbridge, Maidenhead, Berks SL6 0PH. (01628) 804377. Product Licence holder: Cyanamid of Great Britain Limited, Cyanamid House, Fareham Road, Gosport, Hampshire, PO13 0AS. Trade mark. © December 1999 2570/0999

Because you never know
what to expect...



TAZOCIN
piperacillin/tazobactam

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0007-1323(200003)87:3;1-6

A scientific breakthrough in the

Regranex® 0.01% gel (becaplermin).

Revised Prescribing Information.

See refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation: Non-sterile, preserved gel containing becaplermin 100 µg/g. **Use:** To promote granulation and thereby the healing of full-thickness, neuropathic, venous, diabetic ulcers less than or equal to 4 cm².

Dosage: Apply once daily to ulcerated site(s) as a continuous thin layer, using a clean application aid. Cover with a moist saline gauze dressing to maintain a moist wound healing environment. Avoid occlusive dressings. Use in conjunction with standard wound care measures, including initial debridement of all necrotic/infected tissue.

Before use, identify and treat wound-related infection appropriately and exclude or treat underlying conditions such as osteomyelitis or peripheral arteriopathy. Biopsy suspicious ulcers to exclude malignancy. If no meaningful healing evident after first 10 weeks of continuous therapy, re-evaluate treatment and re-assess patient. Continue therapy to maximum of 20 weeks if healing progress seen. Not for repeated use.

Contra-indications: Hypersensitivity to becaplermin or excipients. Known infection(s) at or near ulcer site(s).

Warnings and precautions: Not recommended if under 18 years. If ulcer infection occurs, discontinue until infection controlled. Caution with known malignancies. **Interactions:** Avoid application with other topical medications.

Pregnancy and lactation: Avoid in pregnancy and lactation. **Side effects:** Infection, skin ulceration, skin disorder (including erythema and pain) reported in trials, but not clearly related to REGRANEX.

Bullous eruption and oedema reported rarely. **Overdose:** No untoward systemic effects expected; absorption from application site insignificant. **Packaging:** Laminated polyethylene-lined multi-dose tubes, containing 15g gel.

Pharmaceutical precautions: Store at 2°C–8°C. Do not freeze. Use within 6 weeks of opening.

Legal category: POM. **Marketing authorisation holder:** Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium.

Number in community register of medicinal products: EU/1/99/101/001. **Cost UK:** £275.00 per tube. **IRL:** IRC384.95 per tube. **Further information available from:** Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire HP14 4HJ. UK. **Date of preparation:** July 1999. APIVER 290799.



JANSSEN-CILAG Ltd

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The study included 19 patients observed for a median of 3 years

utions. Tazocin is a broad spectrum
 icidal penicillin for the treatment
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 tive bacteria: - lower respiratory
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 ren 12 years and under. Only recom-
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 ge as for adults with neutropenia
 s weighing < 50kg when 90mg/kg
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 glycoside, is recommended. Renal
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 ssary, please consult data sheet.
 a-indications: Hypersensitivity to
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 yallergic or allergic reaction occurs.
 autions: Periodic assessment of
 , hepatic and haematological func-
 advised. Discontinue if bleeding
 festations occur. Resistant bacteria
 cause superinfection. Convulsions
 occur with higher than recommend-
 ises. Possibility of hypokalaemia in
 nts with low potassium or on cyto-
 s or diuretics. Evaluate patients for
 is prior to treatment for gonor-
 s. Use during pregnancy or lactation:
 if benefit outweighs risk. Side-
 ts: Most frequent gastro-intestinal
 rboances; various skin reactions
 ding rashes, erythema, pruritus and
 aria; allergic reactions: superinfec-
 phlebitis, thrombophlebitis,
 nd inflammation at site of injection,
 frequent muscle pain or weakness,
 cination, dry mouth, stomatitis,
 iting; oedema, tiredness and rarely
 opemia, interstitial nephritis,
 atological changes, increases in
 and rarely renal function test values
 been reported. Overdose:
 acillin may be reduced by dialysis.
 ation: Tazocin 2.25g: Vials con-
 ing piperacillin 2g (as piperacillin
 µm) and tazobactam 250mg (as
 actam sodium). Tazocin 4.5g: Vials
 iring piperacillin 4g (as piperacillin
 µm) and tazobactam 500mg (as
 actam sodium) Basic NHS Price:
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 vial £7.24, PL nos 4.5g strength PL
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what to expect...



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a **CONFIDENT CHOICE** for nosocomial infections

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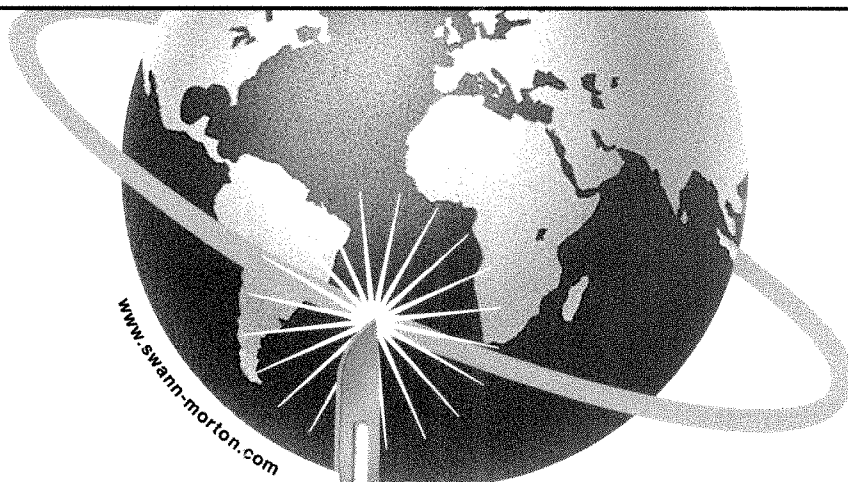
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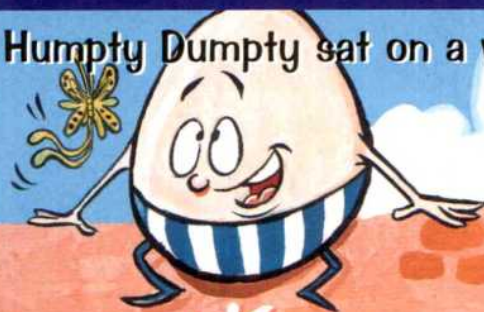
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Evidence-based assessment of severity and management of acute pancreatitis

C. Dervenis and C. Bassi*

First Department of Surgery, Konstantopoulion, Agia Olga Hospital, Athens, Greece and *Department of Surgery, Pancreatic Unit, University of Verona, Verona, Italy

Correspondence to: Dr C. Dervenis

Acute pancreatitis is a potentially fatal disease, with reported mortality rates ranging from zero to almost 25 per cent, depending on severity. Severity itself depends greatly on whether or not pancreatic necrosis is present. The effectiveness of any treatment is related to an ability to predict severity accurately, but there is no ideal predictive system or biochemical marker. While several new therapeutic strategies show real promise in reducing morbidity and mortality rates, disagreement remains regarding the appropriateness of different methods. With this background, a group of specialists in pancreatic disease met recently to review current evidence relating to the assessment of severity and management of the disease¹. An evaluation was made of the strength of available evidence such that different methods of staging and treatment could be placed in one of four categories: proven, probable, possible and inappropriate. These categories are used in this article.

The Atlanta classification is recognized as an important step forward in the management of acute pancreatitis but, with increased use, it has become evident that there is a need for clarification with respect to localized collections of necrotic tissue after necrotizing pancreatitis². Distinction should be made between localized necrotic collections and acute pseudocysts. Although this may be difficult, it is of considerable importance because each diagnosis leads to a different therapeutic strategy; diagnostic error followed by inappropriate treatment is likely to harm the patient. Imaging is mandatory, preferably by a magnetic resonance method and, if a definitive diagnosis cannot be reached, all collections should be considered as localized necrosis until proven otherwise.

As clinical examination in the first 24 h after admission is unreliable in predicting a serious attack of acute pancreatitis, much effort has been made to develop a combination of criteria that might better predict severity. Nevertheless, such combination systems have proved to be of low sensitivity in clinical practice; if a multifactor system is to be used, the Acute Physiology And Chronic Health Evaluation (APACHE) II score calculated at 24 h has proven to be the best choice³. Obesity, indicated by a body

mass index greater than 30, is a reasonably reliable predictor of severe outcome, especially if it is used along with the APACHE II score.

Because the above systems are cumbersome and still less than ideal in terms of accuracy, a number of single risk factors have been evaluated in the clinical setting. These include markers of pancreatic injury and of inflammatory response, together with simple routine tests and imaging methods. Phospholipase A₂ and pancreatitis-associated protein, which are produced and liberated during the initial phase of pancreatic damage, have been confirmed as good early markers of severity. However, their clinical application is inappropriate at present. Activation peptides such as trypsinogen activation peptide and carboxypeptidase activation peptide show great promise as markers of severity, but further development is required before their assay can be useful clinically. A number of markers of immune activation are proven to be (interleukin (IL) 6, IL-8, polymorphonuclear elastase) or are probably (tumour necrosis factor) suitable for the urgent assessment of severity of acute pancreatitis but, again, development of a rapid and reliable test is required. Assay of C-reactive protein is the only easily available blood test in clinical practice that is a proven discriminator of severe and mild disease, at a cut-off level of 150 mg/ml at 48 h after the onset of symptoms⁴.

There is evidence that pleural effusion on an early chest radiograph, which is freely available as a routine test on admission, is probably useful in predicting complications and/or a fatal outcome. More sophisticated imaging, such as enhanced computed tomography (CT), is a proven indicator of pancreatic necrosis with almost 100 per cent sensitivity between days 4 and 10. Further studies are needed to determine its value as an early test for the prediction of severity⁵, and newer scanners and protocols should facilitate this effort.

Acute pancreatitis in its severe form requires urgent treatment in a specialized care centre. By this we mean a hospital with a full complement of the main medical and surgical specialties, facilities for CT, and experienced endoscopists available on a 24-h basis. There is a consensus

that the early restoration of circulatory volume and arterial oxygen tension reduces the risk of complications in this disease, but randomized studies have failed to show any benefit from antiproteases and antisecretory drugs on mortality rate. Although gabexate and somatostatin (and its analogue octreotide) have no effect on mortality rate, they may reduce morbidity, but the evidence is weak.

The value of antibiotics in severe acute pancreatitis has been discussed for many years. Recent controlled trials suggest that there is probably a role for antibiotics in the prevention of complications related to sepsis and, according to a meta-analysis of those trials⁶, in reducing the mortality rate. Current evidence shows that imipenem is superior to other drugs (quinolones) that are able to penetrate pancreatic tissue⁷. Attention should be given to the increasingly encountered fungal infection of pancreatic necrosis secondary to the use of broad-spectrum antibiotics; fungal infection is associated with higher mortality rates. In this context the role of early enteral nutrition should be considered, as recent randomized studies, although small, have shown a reduction in complications and probably in mortality rate⁸.

There is strong evidence that urgent (no later than 72 h from the onset of symptoms) endoscopic sphincterotomy is to be recommended in patients with severe biliary pancreatitis with abnormal liver function; this includes patients with cholangitis⁹. Surgical intervention has a proven role when there are clinical signs of sepsis due to infected pancreatic necrosis. This may be diagnosed by the only reliable test, namely CT-guided fine-needle aspiration followed by Gram staining and culture of the necrotic material. Unroofing of all retroperitoneal collections with thorough debridement is necessary. No single surgical method is superior to the others and the choice should be based on individual experience. There is no evidence in favour of surgery for patients with sterile necrosis¹⁰. Nevertheless, there are subgroups that may benefit from operative intervention. Although difficult to define based on evidence, there is theoretical justification that such subgroups might include patients with continuing deterioration from systemic inflammatory response syndrome despite continuous maximal support, those with a 'septic' picture more than 10 days after the onset of illness, and those with 'refeeding' pancreatitis.

Acute pancreatitis holds out several areas for future investigation through randomized trials. In particular, answers are required to settle controversies surrounding the use of antibiotics and enteral nutrition. The time is ripe too for a re-evaluation of the indications for surgery and of operative techniques.

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Imaging of soft tissue tumours

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In recent times surgeons have been confronted with many advances in imaging technology and, increasingly, the expert advice of our radiological colleagues must be relied upon in order to choose the most appropriate investigations for our patients. However, the recommendations of several authorities for imaging of soft tissue tumours have caused us great concern. Magnetic resonance imaging (MRI) has become the standard for preoperative assessment of soft tissue masses¹⁻³ but a review of the recent literature on the imaging of soft tissue tumours has shown that the best available evidence does not support the current paradigm of MRI superiority over contrast-enhanced computed tomography (CT); the claim that the introduction of MRI has made limb-conserving surgery possible is also false⁴. Limb salvage has, in reality, been made possible through a better understanding of the anatomical relationships and oncological behaviour of these tumours with respect to neurovascular and proximal limb structures, the expanded role of reconstructive procedures and the expert use of preoperative or postoperative radiotherapy.

Heslin and Smith⁵ recently reviewed the data on imaging of soft tissue tumours. They concluded that neither MRI nor CT is able to predict histological subtype or grade of soft tissue sarcomas and that both modalities are equivalent for prediction of tumour size, location and relationship to vital structures. The best available evidence on this issue comes from the Radiology Diagnostic Oncology Group which conducted a prospective, multi-institution, blinded trial to compare state-of-the-art contrast-enhanced CT and MRI in 133 patients⁶. No difference in accuracy was demonstrated for any variable that influences subsequent management decisions. These authors concluded that CT and MRI are equally accurate for local staging of soft tissue tumours in the specific anatomical sites studied. This contrast with earlier opinion was explained by improvement in technology since initial conclusions were reached over a decade ago^{7,8}.

One is frequently referred patients whose MRI findings have been accepted without clinical (and in some cases without histological) correlation. The reality is that most soft tissue lesions remain non-specific, a correct histological diagnosis being reached on the basis of imaging studies alone in only 25-35 per cent of cases⁹. A number of issues cause concern. First, many radiologists are inexperienced in the interpretation of soft tissue masses on MRI. Errors in

judgement arise particularly when peritumoral oedema is mistaken for tumour infiltration, resulting in overestimation of tumour extent. Kransdorf and Murphy¹⁰ suggest that MRI short T₁ inversion recovery sequences should only be used for subtle areas of soft tissue abnormality as they increase lesion conspicuity, but this is not widely appreciated by many radiologists. The best available evidence suggests that tumour diameter (for T₁ tumours) is determined accurately, compared with histological size, in 87 per cent of MRI and 83 per cent of CT scans, with both tending to overestimate⁶. A second concern is that MRI has become favoured because of a presumed greater accuracy in defining tumour relationship to neurovascular structures. Panicek *et al.*⁶ suggest that MRI has low positive predictive values for vascular and nerve involvement (10 and 6 per cent respectively); CT has similarly poor values (27 and 25 per cent respectively). These high false-positive rates are not widely recognized and potentially disastrous situations may arise in which patients are recommended either unnecessary amputation or unnecessary neoadjuvant therapy. A third worry is that the claim that MRI is superior for the evaluation of anatomical compartment and individual muscle involvement⁸ has not been substantiated in the large 1997 study by Panicek *et al.*⁶

In conclusion, the best available evidence is contrary to the commonly accepted wisdom that MRI is superior to CT in the assessment of soft tissue tumours. Major management decisions must not be based on imaging alone. Imaging determines the site and extent of the lesion, along with the proximity of nearby structures. Clinical assessment by experienced specialists, appropriate biopsy and multidisciplinary review are together of at least equal importance in the management of these tumours.

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Where can surgeons publish?

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'The unpublished manuscript is like an unconfessed sin that festers in the soul, corrupting and contaminating it' – Antonio Machado.

In the last two issues of the Journal you were told *why*¹ and *what*² a surgeon might publish. This article will suggest *where* you can publish whatever publishable material you have. Which target journal is a decision you have to take at the start, *before* starting to hammer the typewriter keys. When doing the actual writing you have to address the audience you are catering for and keep in mind the specific requirements of the journal you chose. Is your aim to 'sell' a 'new operation' to the general practitioners in your country? In that case you have to emphasize basic concepts. If your purpose is to increase your fame within the surgical community then you can afford to be more technical.

You worked so hard on your study (or so you think) and now you want it to reach the greatest possible and the most prestigious readership, and to have maximal impact. How sweet it could be, strolling around the hospital and repeatedly hearing 'Hey Dr Jones, your *New England Medical Journal* article is superb!' But is your article publishable in such a leading journal? If not, where is it publishable?

Chief goals when looking for a suitable venue for your manuscript

- The greatest readership. Do you wish to bury your *magnum opus* in a 'prestigious' journal that nobody reads?
- An 'interested' readership. You do not want to describe your recent technical innovation to medical gastroenterologists.
- A 'prestigious' journal (high 'impact'). Do not forget – one of the chief reasons for you to publish is the want of prestige¹.
- Maximize chances and speed of acceptance. How depressing it is to submit a 'classic' to a journal that takes a year to reject it.
- Minimize rejections and need for prolonged efforts at 'recycling'. Ideally, you want your manuscript to be accepted on the first submission. In reality, a mean of two

rejections per manuscript is what you have to live with, unless you are a renowned surgical Shakespeare.

These goals do not always go together. A journal may be 'prestigious–high impact' but attract only a small, narrow-focused readership (e.g. *Journal of Endovascular Surgery*; impact factor (IF) 4.377) or it may have a wide readership, which is, however, not interested in the topic discussed. When 'shopping' for a journal, the manuscript is your merchandise. You have to understand the 'publishing market' and be able to assess the 'value' of your manuscript; only then will it be possible to tailor your manuscript to the individual journal and thus achieve the goals.

The 'market' for the surgical manuscript

Professional journals, as any other commodity, can be graded into 'classes'. The car market has its Rolls Royce, Mercedes, Fords, Toyotas and even Fiats. Which journal is the Jaguar and which the VW Beetle? At this point you should understand the concept of the IF. This is used by the scientific community to score the 'prestige' of individual journals and thus the 'academic value' of the papers published in them. The IF of a journal is calculated as the ratio of the number of citations of articles published over 2 years (in the whole literature) to the number of articles published over 2 years (by a journal). In simple terms, the more cited the journal, in other publications, the higher its IF. A journal that publishes a relatively small number of novel–momentous papers will have a high IF while a journal accepting a lot of 'non-significant' material is doomed in terms of IF. It is easy to imagine the existence of two separate vicious circles. One involves a high IF journal (e.g. *New England Journal of Medicine*; IF 28.660) which, because of its conceived prestige, attracts the best manuscripts from most qualified investigators and rejects all that is inferior. Its publications are 'best-sellers' and highly quoted across the world, thus further increasing the IF. On the other hand, a 'modest' journal such as the *European Journal of Surgery* starts with a much lower IF (0.795) and consequently attracts manuscripts of 'lesser value', and may be forced to publish papers rejected by others. The latter are poorly cited thus the journal's IF remains low. While it is very difficult to improve a journal's IF, it is very easy to lose it by poor

Table 1 The market for surgical publishing

	Impact factor
Class I. 'General top four' Leading, high-impact and widely read international journals serving all specialties	
<i>New England Journal of Medicine</i>	28.660
<i>Lancet</i>	11.793
<i>JAMA</i>	9.552
<i>British Medical Journal</i>	5.325
Class II General surgical journals	
IIA Top group: leading, high-impact and widely read (worldwide) general surgical journals	
<i>Annals of Surgery</i>	5.405
<i>Archives of Surgery</i>	2.526
<i>British Journal of Surgery</i>	2.381
<i>World Journal of Surgery</i>	2.271
<i>Surgery</i>	2.243
<i>American Journal of Surgery</i>	1.874
<i>Journal of the American College of Surgeons</i>	1.872
<i>Annals of Surgical Oncology</i>	1.811
<i>Journal of Surgical Research</i>	1.362
<i>Journal of Surgical Oncology</i>	1.023
IIB. Intermediate group	
<i>American Surgeon</i>	0.994
<i>Arch Langenbeck Surgery (German)</i>	0.970
<i>European Journal of Surgical Oncology</i>	0.958
<i>Der Chirurg (German)</i>	0.932
<i>Hepatogastroenterology</i>	0.925
<i>Annals of the Royal College of Surgeons of England</i>	0.827
<i>European Journal of Surgery</i>	0.795
<i>Surgical Oncology</i>	0.717
<i>Annales de Chirurgie (French)</i>	0.606
<i>Canadian Journal of Surgery</i>	0.570
<i>Australian and New Zealand Journal of Surgery</i>	0.536
<i>Journal of the Royal College of Surgeons of Edinburgh</i>	0.434
<i>Zentralblatt Chirurgie (German)</i>	0.425
<i>International Surgery</i>	0.388
<i>Surgery Today</i>	0.303
IIC. 'Bottom' group	
<i>Digestive Surgery</i>	0.275
<i>Acta Chirurgica Belgica (French)</i>	0.260
<i>Minimally Invasive Therapy</i>	0.255
<i>Journal de Chirurgie (Paris) (French)</i>	0.193
<i>South African Journal of Surgery</i>	0.129
<i>Contemporary Surgery</i>	—*
<i>Current Surgery</i>	—*
<i>Surgical Rounds</i>	—*
<i>Journal of Surgical Infections</i>	—*
Class III Subspecialty journals	
IIIA Top group: leading, high-impact and widely read (worldwide) subspecialty surgical and 'surgical interest' journals	
<i>Gastroenterology</i>	10.330
<i>Journal of Endovascular Surgery</i>	4.377
<i>Critical Care Medicine</i>	3.745
<i>Cancer</i>	3.660
<i>Transplantation</i>	3.522
<i>Journal of Thoracic and Cardiovascular Surgery</i>	2.954
<i>Journal of Vascular Surgery</i>	2.674
<i>Shock</i>	2.572
<i>Annals of Thoracic Surgery</i>	2.190
<i>Diseases of the Colon and Rectum</i>	2.138
<i>Surgical Endoscopy and Ultrasonography</i>	2.103

Table 1 Continued

	Impact factor
IIIB. Lower group	
<i>Journal of Trauma</i>	1.444
<i>Obesity Surgery</i>	1.360
<i>Journal of Pediatric Surgery</i>	1.114
<i>Surgical Laparoscopy and Endoscopy</i>	0.974
<i>Journal of Laparoendoscopic Surgery</i>	0.968
<i>Vascular surgery</i>	0.627
Class IV. 'Local' journals: general or specialty journals published in your country, usually in your language	

*New journals, not as yet cited by the Journal Citation report. The list of journals is not inclusive. A grading of journals using the impact factor is prone to bias as explained in the text. To access the web page on any of the listed journals go to Land of Medical Links by Joe Bunker: <http://alexia.lis.uiuc.edu/~bunker/journals.html>

Table 2 What is the 'value' of your manuscript?

Level	Description	Example	Submit to
I	Groundbreaking discovery, high level of evidence; if reconfirmed may radically change clinical practice	'A new operation for anal incontinence – 5 years' follow-up in 500 patients' or 'Laparoscopic versus conventional Whipple procedure: a prospective randomized trial in 200 patients'	Class I or IIA journals (see Table 1)
II	Novel and/or well performed piece of research that may significantly change current thinking or modify (or enhance) clinical practice	'Gene transfer therapy of hepatic cancer' or 'Conservative versus operative treatment of recurrent acute diverticulitis: a prospective randomized study with a 3-year follow-up' or 'The value of preoperative bowel preparation – a meta-analysis'	Class IIA or IIIA journals (see Table 1)
III	A solid piece of research that sheds new light or confirms/disputes what is already known	'Faecal diversion is not necessary in low anterior resection of the rectum – experience in 99 patients'	Class IIA, IIB, IIIA or IIIB journals (see Table 1)
IV	A 'nice little study', local experience with a known entity or a 'reminder' about a rare condition	'Upper gastrointestinal bleeding in Scandinavia' or 'Acute appendicitis after appendectomy – report of five cases'	Class IIC or IV journals (see Table 1)

editorial performance. The IF as a gauging instrument is far from perfect: it favours English-language, 'large specialties', the USA and journals with fewer articles. It hinders predominantly clinical journals. Table 1 shows the IF of different journals classified into a number of groups, based on the IF and a personal perception of the surgical 'publishing market'.

Whether the IF has any impact on readers has hitherto received very little attention. In a Chinese study of library journal use there was a significant correlation between frequency of use and IF³. An assessment of journals used at a Chicago medical library found that certain journals may be popular to the general reader, for educational and clinical purposes, but not to the local faculty for research purposes⁴. In a recent survey on what American surgeons read (M. Schein *et al.*, unpublished data) it was found that IF correlates only partially with the 'importance' attributed to

the various journals by surgeons. Other factors were important; for example, certain journals are 'forced' on surgeons as part of a membership package of large surgical associations.

What is the value of your manuscript?

To most writers, especially the novice, a recently completed study seems a potential masterpiece, which deserves the best venue and audience. (Only last week one of our residents in New York suggested that his humble series of three 'unusual' cases should be written up for the *Lancet*.) To maximize the chances of acceptance of your alleged 'masterwork' you have to assess its quality. This should provide a realistic view of the value of the paper and direct you to the right journal. For example, a retrospective clinical series is not going to get published in the *New*

England Journal of Medicine. In Table 2 a practical classification of 'original studies' is proposed. The latter, however, should not be lumped together with 'review articles' or 'technical notes' but the value of each should be assessed within its own kind.

How to select the right journal for your manuscript

When you know how to assess the prestige of the various journals and can estimate objectively the worth of your work, how easy is it to correctly match the two together? It is difficult and requires experience but the following is a practical advice list.

- Choose the audience—general, specialized or local? If you have data for a level II paper (Table 2) on surgical gastroenterology, you may aim for the top of class IIA journals (Table 1), reaching the cream of surgical readership. Alternatively you could select a leading class IIIA subspecialty journal (Table 1) in gastroenterology, targeting mainly those interested in this field, surgeons and non-surgeons.
- Consult the 'instructions to authors'. These are available in each journal. See what type of manuscript they prefer. Read the aims and objectives or mission statement of the journal. All journals welcome 'original' clinical and laboratory studies but only some consider review articles, pure technical notes or case reports. Only a few accept non-commissioned editorials. Studying the instructions to authors is a *sine qua non*. Submitting an unsuitable manuscript results in an automatic rejection. At this stage you may short list a few journals for an in-depth analysis.
- Browse through the journals. See what type of papers they published over the past year. Would your manuscript fit the ethos and style of that journal?
- If the journal has already published one or two articles on 'your topic', you might want to go elsewhere. If your paper can solve the problem raised by a previous article in that journal, go ahead.
- Some surgeons make a habit of submitting all their papers to one journal or a limited list of journals. This may not be a bad idea as they gradually learn how to satisfy the needs of these journals while the latter become familiar with them.
- Get advice. Choosing a journal for your manuscript is an art that is acquired during many years of submission–rejection, trial–error cycles. As editorial reviewers for a

number of journals, we often see manuscripts that are misdirected into the 'wrong' journal. This represents a waste of efforts by the authors, reviewers and journal editors, which could be avoided if the author first consults an experienced and well published surgeon in their environment. A well published and well read surgeon has a 'publishing judgement' which, like clinical judgement, is difficult to express in any algorithm. His skills allow him to penetrate into the mind of the various journal editors and reviewers, guessing what they like and what they dislike. He knows which journals are 'rigid-traditional' and which would consider 'innovative' styles. He knows the assessment–rejection cycle of the individual journals and can advise you how high to start and how to continue, maximizing the rate of eventual acceptance and its speed. If no such an expert is available in your vicinity try elsewhere; no surgeon would refuse to give advice to a young colleague. Journal editors themselves may give you an informed view of a proposed article.

Getting your paper published is a complex task, which is becoming increasingly difficult. Only a few decades ago prestigious journals published long manuscripts based on three clinical cases; now you cannot publish the most interesting case reports outside local or 'throw-away' journals. Rejection rates are extremely high, e.g. 80 per cent for the *BJS*. A key element of a successful submission is choosing the right journal. Assess the value of your manuscript, know the publishing market, study the target journals and get learned advice.

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Committee on Publication Ethics

GUIDELINES ON GOOD PUBLICATION PRACTICE

3 Authorship

Definition

There is no universally agreed definition of authorship, although attempts have been made (see Appendix, January 2000 issue, page 7). As a minimum, authors should take responsibility for a particular section of the study.

Action

- 1 The award of authorship should balance intellectual contributions to the conception, design, analysis and writing of the study against the collection of data and

Other sections of these guidelines will appear in future issues. The full guidelines are available at www.publicationethics.org.uk.

other routine work. If there is no task that can reasonably be attributed to a particular individual, then that individual should not be credited with authorship.

- 2 To avoid disputes over attribution of academic credit, it is helpful to decide early on in the planning of a research project who will be credited as authors, as contributors, and who will be acknowledged.
- 3 All authors must take public responsibility for the content of their paper. The multidisciplinary nature of much research can make this difficult, but this can be resolved by the disclosure of individual contributions.
- 4 Careful reading of the target journal's *Advice to Authors* is advised, in the light of current uncertainties.

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Warfarin induced skin necrosis

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Background: Warfarin induced skin necrosis is a rare complication with a prevalence of 0.01–0.1 per cent. It was first described in 1943.

Methods: A literature review was undertaken using Medline; all relevant papers on this rare complication of warfarin therapy were used.

Results: There are several adverse skin manifestations associated with the use of oral anticoagulants, ranging from ecchymoses and purpura, haemorrhagic necrosis, maculopapular vesicular urticarial eruptions to purple toes. This article concentrates mainly on warfarin induced skin necrosis. The syndrome typically occurs during the first few days of warfarin therapy, often in association with the administration of a large initial loading dose of the drug. Although the precise nature of the disease is still unknown, advances in knowledge about protein C, protein S and antithrombin III anticoagulant pathways have led to a better understanding of the mechanisms involved in pathogenesis. Differential diagnosis between warfarin induced skin necrosis and necrotizing fasciitis, venous gangrene and other causes of skin necrosis may be difficult; the disease may also be confused with other dermatological entities.

Conclusion: Warfarin induced skin necrosis, while rare, is an important complication. All surgeons should be aware of its existence.

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Introduction

Since the introduction of oral anticoagulants in the 1940s, warfarin (coumadin) has become one of the most important drugs used in both surgical and medical practice. Its common uses include management of deep venous thrombosis and pulmonary thromboembolism, prophylaxis in patients with various arterial bypass grafts, as well as control of embolism associated with cardiac dysrhythmias and prosthetic heart valves. Warfarin induced skin necrosis is a rare side-effect and is estimated to occur in only 0.01–0.1 per cent of patients taking the drug^{1,2}; to date only about 300 cases have been reported worldwide. In the literature the condition is sometimes referred to as 'coumarin induced skin necrosis', but this term is inappropriate as coumarin is the parent compound from which warfarin, and many other oral anticoagulants, are derived. Coumarin itself lacks anticoagulant activity³.

Although its precise pathogenesis is still unclear, warfarin induced skin necrosis is a well established condition of which all clinicians should be aware. The associated morbidity is high, frequently requiring surgical interven-

tion with wide local debridement, skin grafting or even amputation. Failure of early diagnosis and treatment may result in death.

Historical background

Warfarin induced skin necrosis was originally described in 1943⁴, when breast necrosis in a 49-year-old woman was mistakenly attributed to thrombophlebitis migrans disseminate; the connection with the medication bis-hydroxycoumarin was not made until 1950. In 1954, Verhagen⁵ was the first to associate skin necrosis with oral anticoagulants, based on 13 cases from the Netherlands. The first cases in the USA were reported in 1961⁶, and since then approximately 300 cases have been reported worldwide.

Clinical presentation

Warfarin induced skin necrosis is often heralded by paraesthesia, or a sensation of pressure, associated with an erythematous flush that is usually poorly demarcated. The lesions are painful, sudden, well localized and initially

haemorrhagic or erythematous. Accumulation of oedema in the dermis and subcutaneous tissues produces a peau d'orange effect which demarcates the geographical border of the lesion. Over the first 24 h, petechiae and haemorrhagic bullae within the borders of the involved skin may occur⁵⁻⁷ (Fig. 1). The development of these haemorrhagic bullae signals irreversible injury and full-thickness skin necrosis is the inevitable end stage⁵⁻⁸. The eschar eventually sloughs, revealing a defect extending deep into the subcutaneous fat. Small lesions may be treated conservatively and heal by granulation and scarring, but more extensive lesions require surgical debridement and skin grafting, or amputation.

The condition develops mainly in middle aged women, who are usually perimenopausal, obese and being treated for deep vein thrombosis or pulmonary embolism⁹. The reason for this female preponderance is unclear. The first symptoms of skin injury usually appear 1–10 days after the initiation of warfarin therapy, and the majority of lesions appear within an interval from the third to the sixth day. The disease is also reported occasionally to occur up to 15 years after the start of therapy¹⁰, but in such circumstances it is sometimes unclear whether the skin necrosis is due to warfarin or to another cause. As the level of anticoagulation might fluctuate during a long treatment period, the diagnosis must still be considered¹¹.

In women, the site of the lesion is random and unpredictable, but the breast is the most common site, followed by the buttocks and thighs¹². Occasionally, the trunk, face and extremities are also involved¹³. In men with skin necrosis involvement of the breast is rare; sometimes the penile skin may be affected¹³. There are reports of patients whose lesions have healed spontaneously after the discontinuation of warfarin; they did not always reappear



Fig. 1 Extensive bruising and skin necrosis on the torso of a patient receiving warfarin therapy

after restarting the drug¹⁴. Of the 58 cases of warfarin induced skin necrosis reviewed by Jillella and Lutchter in 1996¹⁵, oral anticoagulation was resumed in seven. Four of these seven patients developed a recurrence of skin lesions and the authors suggested that warfarin can be resumed on a trial basis if long-term anticoagulation is absolutely necessary. It is also worthy of note that recurrence of skin lesions may sometimes occur in the absence of further anticoagulation therapy¹⁶.

Allergic dermatitis is another rare complication of warfarin therapy¹⁷. This has various clinical manifestations, including urticaria¹⁸, maculopapular erythematous rash¹⁹ and vesicular rash²⁰, with an onset days to months after starting warfarin. These lesions commonly disappear when warfarin is stopped, but may reappear upon rechallenge^{19,20}.

Histopathology

Since biopsies are usually taken at a late stage, little is known about the early histological changes that occur before gross tissue necrosis. The diagnosis is, therefore, made mainly on clinical grounds. Early pathological changes are microvascular injury with fibrin deposits in the postcapillary venules and small veins^{8,17}, and with haemorrhage and diffuse necrosis in the dermis and subcutaneous fat. Although a few specimens show histological evidence of acute inflammation with perivascular neutrophils and lesions resembling vasculitis²¹, this is uncommon. Most specimens show a distinctive lack of vascular or perivascular inflammation, as well as a lack of arteriolar thrombosis.

Gross and microscopic lesions, virtually identical to those of warfarin induced skin necrosis, have been described in renal patients with calciphylaxis, a condition characterized by soft tissue calcification in those on haemodialysis²². Patients with purple toe cholesterol embolization syndrome²³, cryofibrinogenaemia²⁴, lupus anticoagulant-associated skin necrosis²⁵ or pyoderma gangrenosum²⁶ may develop similar lesions. Clinicians must also be careful to rule out all other causes of acute thrombosis with associated skin necrosis, including acute necrotizing fasciitis, disseminated intravascular coagulopathy with purpura fulminans, formation of heparin induced antiplatelet antibodies, ecthyma, cellulitis and Fournier's gangrene. The clinical history and cutaneous distribution may help to distinguish between these conditions and warfarin induced skin necrosis.

Aetiology and pathogenesis

What determines which patients will actually develop skin necrosis is unknown; the aetiology of the disease is still

obscure. Thrombosis, hypersensitivity, haemorrhage, factor VII deficiency, protein C deficiency and a direct toxic effect of warfarin have all been suggested as potential pathophysiological mechanisms^{1,8}. When the histology is reviewed carefully, some lesions are noted to exhibit islands or peninsulas of normal tissue within a zone of necrosis. For this reason, some authors propose that arteritis or vasculitis may be the underlying cause²⁷.

Despite the apparent brief interval between exposure to warfarin and the cascade of events that lead to the skin lesions, the theory of a hypersensitivity reaction being the underlying event²⁸ is not widely accepted. Indeed, this unproven hypothesis has never seemed likely. Allergic reaction to warfarin was evaluated by performing skin tests with the drug on patients with a history of warfarin induced skin necrosis and none developed immediate or delayed reactions²⁹.

Nalbandian *et al.*⁹ proposed that warfarin had a direct toxic effect at the junction of the precapillary and the arterial capillary of the dermovascular loop. According to this theory, warfarin injured capillaries dilate and then rupture, and the resulting haemorrhage appears as petechiae that coalesce into ecchymoses. Finally, dermal venules and veins distal to the injured capillaries thrombose owing to stasis of blood flow, and tissue necrosis occurs. Experiments have substantiated this theory. Widespread vascular dilatation, endothelial swelling and proliferation, and vessel necrosis and rupture are found in dogs given lethal doses of dicumarol³⁰. However, once skin damage has occurred, new lesions rarely develop despite continuing warfarin therapy.

Ever since the condition was first recognized, it has been noted that the overwhelming majority of cases occur in patients being treated for deep vein thrombosis or pulmonary emboli; those taking warfarin for cardiac indications, such as atrial fibrillation, or for cerebral vascular insufficiency rarely develop skin necrosis³¹. A possible link between warfarin induced reductions of vitamin K-dependent proteins and skin necrosis began to receive attention in the 1970s, even before the isolation of protein C and protein S³². Protein C deficiency has received particular attention^{33–35}, and hereditary protein C deficiency is considered a major risk factor. However, this is not the sole risk factor, as other hypercoagulable conditions in patients with protein S deficiency³⁶, factor V Leiden³⁷, antithrombin III deficiency³⁸ and lupus anticoagulant³⁹ have been associated with skin necrosis. The association with protein C deficiency has led to the theory that a sudden decrease in protein C activity may precipitate warfarin induced skin necrosis, and that patients with such a deficiency are at increased risk of this complication.

Predisposing factors

Protein C deficiency

Protein C is 62 000-kDa vitamin K-dependent glycoprotein that is an important regulator of the coagulation and fibrinolytic systems. It circulates as an inactive zymogen in blood at a concentration of 4 µg/ml. The rate of activation of protein C by thrombin, the only known physiological activator, is enhanced several thousandfold by a cofactor on the surface of vascular endothelium, termed thrombomodulin. Once generated, activated protein C proteolytically inactivates factor VIIIa and factor Va, thereby inhibiting the conversion of factor X to factor Xa and prothrombin to thrombin respectively. Protein S enhances the binding of activated protein C to phospholipid membranes and accelerates the inactivation of factor VIIIa and factor Va⁴⁰.

A low level or absence of protein C is associated with recurrent familial thrombosis and requires long-term anticoagulation with warfarin to prevent thromboembolic problems. Protein C deficiency, first described in 1981, is a hereditary coagulation disorder manifested by a thrombotic tendency of variable severity⁴¹. It is inherited as an autosomal dominant trait and heterozygotes present with what are essentially venous thrombotic manifestations; these may be of early or late onset, probably depending on different degrees of expressivity^{42,43}. It is therefore common for those affected to be on warfarin therapy.

Skin necrosis has been reported in protein C-deficient patients receiving warfarin, but evidence of an association is based on scattered case reports and small series. In a series of 16 patients with warfarin induced skin necrosis, only five were protein C deficient⁴⁴ and most of these patients had been given a very large loading dose of acenocumarol (80 mg).

The mechanism is thought to be that, following the initiation of warfarin, both protein C antigen and activity levels drop rapidly, compared with levels of other vitamin K-dependent factors such as factors IX and X, and prothrombin⁴⁵. This observed rapid early fall in protein C level prompted the hypothesis that the administration of warfarin to protein C-deficient individuals causes a temporary exaggeration of the imbalance between pro-coagulant and anticoagulant pathways³³; that is, the early suppressive action of warfarin on protein C may not be counterbalanced by the anticoagulant effect created by the decline in other vitamin K-dependent factors, thereby leading to a relative hypercoagulable state at the start of treatment. This leads to thrombotic occlusions of the microvasculature with resulting necrosis. This may explain the usual early onset of most lesions. Occasional cases of late appearance in the course of therapy may be due to

intermittent non-compliance, and the appearance of skin lesions after the reintroduction of warfarin⁴⁶.

Protein S deficiency

Protein S is a vitamin K-dependent cofactor for activated protein C. Patients who are deficient in protein S are at increased risk of thromboembolic disease. Only a few cases of skin necrosis have been associated with protein S deficiency, in both its congenital and acquired form^{47,48}. Many of the patients with acquired protein S deficiency have end-stage renal failure, requiring continuous ambulatory peritoneal dialysis or haemodialysis⁴⁹; some also have antiphospholipid antibody syndrome⁵⁰.

Antithrombin III deficiency

The function of antithrombin III is to neutralize thrombin and to inactivate other serine proteases, such as activated factors IX, X, XI and XII⁵¹. There have been only a few cases of warfarin induced skin necrosis in patients with antithrombin III deficiency. The potential increased generation of thrombin at the beginning of warfarin treatment without the neutralizing effects of antithrombin III creates a transient hypercoagulable state in these patients; this may cause thrombosis of the dermal vasculature and contribute to skin necrosis⁵².

Prevention

The clinician should be aware of the existence of warfarin induced skin necrosis and should be attuned to a patient's early complaints of localized skin discomfort, especially in the breast, buttock and thighs, even in the absence of overt signs. Advice from haematologists who may be familiar with the management of the condition is helpful. The population at greatest risk comprises acutely ill women started on warfarin for treatment of thromboembolic disease^{1,13}. Screening of patients for protein C or S or antithrombin III deficiencies before beginning warfarin therapy may delay treatment and cannot generally be recommended. In any event, these tests are neither sensitive nor specific in predicting a risk of developing this complication.

Using progressively increasing doses of warfarin over an extended period may be considered in patients deemed to be at risk⁵³. Large loading doses of warfarin should be avoided. This anticoagulation plan promotes a more gradual decline in protein C level, towards a rate similar to that of the other longer-lived vitamin K-dependent coagulant factors, such as factor IX and prothrombin. The putative hypercoagulable state^{33,45} at the initiation of warfarin therapy may thereby be avoided. This method may be applicable to all

patients at risk who require long-term anticoagulation with warfarin.

Rapid reversal of warfarin with high doses of parenteral vitamin K and therapeutic heparin anticoagulation may also prevent the progression of skin necrosis⁵⁴. However, the clinician should be aware that the administration of heparin itself, whether intravenously or subcutaneously, may cause a skin necrosis that is clinically indistinguishable from the warfarin induced version^{55,56}. Heparin induced skin necrosis often appears between the fifth and tenth day after beginning treatment. The microscopic picture is similar to that of the warfarin variety, involving thrombosis of dermal venules and capillaries⁵⁷. There is a predilection for the abdominal wall, upper and lower extremities, the nose and dorsum of the hands⁵⁸. Further discussion of heparin induced skin necrosis is beyond the scope of this article.

Treatment

Once the signs of irreversible skin injury are apparent, there is no convincing evidence that the various therapeutic approaches affect eventual outcome⁷. Nevertheless, it is possible to prevent progression of skin necrosis if patients are carefully monitored in the initial phases of treatment so that excessive doses of warfarin are avoided and vitamin K is administered in the early stages of lesion development⁵⁴.

In those with protein C deficiency, intravenous infusion of monoclonal antibody-purified protein C concentrates may be used with good effect^{59,60}. However, this cannot be recommended as long-term routine treatment because of its high cost. Stopping or continuing warfarin does not alter the healing or the progression of the eschar⁹. After the cessation of warfarin, anticoagulation should be achieved by intravenous heparin therapy until the necrotic lesions are healed⁹. Studies have suggested benefit from the use of low molecular weight heparin, which consists of fragments of the heparin chain that have a high affinity for antithrombin III and possess the antithrombin action (antifactor-Xa) of standard heparin but with less anticoagulant activity (thrombin inhibition) than standard heparin⁶¹. Even though heparin may be associated with skin necrosis, there is no report in the literature of necrosis following the institution of heparin after the occurrence of warfarin induced skin necrosis.

Although extreme caution should be taken, the commencement of warfarin has been managed successfully in some patients^{15,35}. In order to sustain levels of protein C during the critical initiation of warfarin, the starting dose in these circumstances should be very low and gradually increased by 1–2 mg a day until the desired international normalization ratio has been achieved over a period of about

10 days^{42,43,62}. Careful monitoring of patients in this situation is mandatory.

Prostacyclin has been used in the treatment of warfarin induced skin necrosis with a resulting clinical and histological improvement⁶³. Prostacyclin is an arachidonic acid metabolite produced by endothelial cells in arteries, veins and the microcirculation; it is a potent vasodilator and inhibitor of platelet aggregation. It has been used successfully in the treatment of a variety of vascular and thrombotic disorders, and further studies of its use in warfarin induced skin necrosis seem indicated.

Despite best medical treatment, about half of the patients with skin necrosis will ultimately require surgical intervention and the plastic surgeon is frequently consulted. Surgical treatment involves the eradication of local sepsis with topical antimicrobial agents, such as silver sulphadiazine⁶⁴. Some patients require extensive surgical debridement of the necrotic lesions or even amputation of the affected extremity^{65,66}. Most skin necrosis heals with time, but some of the larger lesions leave considerable subcutaneous induration. Although such areas may no longer be painful⁶⁷, skin grafting may still be required in some cases.

Conclusion

Although warfarin induced skin necrosis poses a difficult diagnostic problem, knowledge of the condition should allow the clinician to make an early diagnosis. It is particularly important to differentiate warfarin induced skin necrosis from the venous gangrene that results from extensive deep venous thrombosis (phlegmasia cerulea dolens) and is itself an indication for anticoagulation⁶⁸. Non-invasive imaging techniques, such as arterial and venous duplex scans, may be useful. The occurrence of occasional cases of skin necrosis should not, however, outweigh the vast body of evidence of the benefit of warfarin in the treatment of many diseases, nor should it preclude the possibility of future reintroduction of oral anticoagulation if there is a real indication.

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Pain after laparoscopic cholecystectomy

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Background: Although laparoscopic cholecystectomy (LC) results in less pain than open cholecystectomy, it is not a pain-free procedure. Many methods of analgesia for pain after laparoscopy have been evaluated.

Methods: Forty-two randomized controlled trials assessing interventions to reduce pain after LC are reviewed, as are the mechanisms and nature of pain after this procedure.

Results: Non-steroidal anti-inflammatory drugs, wound local anaesthetic, intraperitoneal local anaesthetic, intraperitoneal saline, a gas drain, heated gas, low-pressure gas and nitrous oxide pneumoperitoneum have been shown to reduce pain after LC. The clinical significance of this pain reduction is questionable.

Conclusion: Pain after LC is multifactorial. Although many methods of analgesia produce short-term benefit, this does not equate with earlier discharge or improved postoperative function. However, single trials evaluating low-pressure insufflation, heated gas and multimodal analgesia suggest that clinically relevant benefits can be achieved.

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Introduction

A major benefit of laparoscopy in upper gastrointestinal surgery results from avoidance of an upper abdominal incision. Less pain and improved pulmonary function tests are proven benefits of laparoscopic cholecystectomy (LC) compared with small-incision cholecystectomy^{1–3}. However, assessment of postoperative stay and return to normal activity has shown conflicting results^{2–4}. Many trials have assessed methods of reducing the pain that is experienced after LC and several aspects of pain after laparoscopy have been reviewed previously^{5–7}. These reviews have concentrated on the mechanism of pain^{6,7} or focused on gynaecological procedures, with emphasis on the role of non-steroidal anti-inflammatory drugs (NSAIDs)⁵. The aim of the present paper is to review all randomized controlled trials that have addressed pain after LC. The heterogeneity of interventions to reduce pain prevents the analysis of data as a quantitative systematic review. The nature and severity of pain after LC, and the mechanisms of pain related to laparoscopy are also discussed.

Methods

A computerized Medline search was performed with the key words 'pain', 'cholecystectomy/laparoscopic', 'pneumoper-

itoneum' and 'laparoscopy' for the interval January 1990 to June 1999. The bibliographies of the retrieved articles were reviewed to obtain other relevant papers. Non-randomized studies and abstracts were obtained but they are not incorporated in this review unless they provide information not covered in published randomized trials. Language restriction was not applied but it was not possible to obtain every non-English language article^{8,9}. Articles in French, Japanese and German were translated. Forty-two randomized controlled trials assessing various interventions for their ability to reduce pain after LC were retrieved. Studies reported to be randomized were included if pain was evaluated prospectively and the outcome was compared with that of a control group.

Reviewed articles

Quality

It is not the purpose of this review formally to evaluate the quality of the included randomized trials. However, major deficiencies in individual trials are discussed in the text. A review of the quality of randomized controlled trials involving laparoscopic surgery¹⁰ concluded that only 15 per cent of trials could be classified as well

conducted. Similarly, the majority of trials reported in this review contain methodological deficiencies. Although some are generally of good quality, none of the reviewed trials complies fully with the CONSORT (consolidated standards of reporting trials) guidelines¹¹, even those published after these recommendations became available in 1996. Deficiencies include an inadequate description of randomization methods^{12–16}, failure to report inclusion and exclusion criteria^{12,15,17,18} and non-blinded evaluation of endpoints^{15,19,20}. Only a few trials made attempts at prospective evaluation of sample size^{21–25}. Methods used to evaluate pain are sometimes not described adequately¹⁵. Follow-up is often limited to a short postoperative period^{17,23,26}. Some studies fail to mention methods of restriction of randomization, but obtain multiple groups of equal numbers^{13,15,16}. This raises serious concerns about the adequacy of sequence generation and concealment, a problem noted in reports of gynaecological randomized controlled trials²⁷, and satisfactory in only 50 per cent of general surgical trials¹⁰.

Assessment of pain

Most trials assessing pain after LC use a visual analogue scale (VAS) or verbal rating scale. These scores show a high level of correlation^{16,28,29} although the VAS is thought to be more sensitive for detection of small differences in pain levels. However, increasing the number of response categories does not necessarily make a test more sensitive or valid because patients become confused by too many options or do not understand the instructions²⁹. VAS measurement in the immediate postoperative period can be unreliable with any individual score having an imprecision of ± 20 mm³⁰; its use in the recovery unit is therefore questionable.

Most methods of pain measurement are subject to the problem of results being affected by the timing of administration of analgesia. The use of patient-controlled analgesia (PCA) helps remove this variable and also provides valid comparison of analgesic requirements, which is not possible with nurse-administered analgesia³. Because of early discharge after LC, PCA devices are seldom instituted in clinical practice and are used infrequently in pain trials relating to LC^{3,17,21}.

The statistical analysis of VAS is also controversial; some authors analyse the data as parametric^{31,32}, although most treat the values as non-parametric³³. It has been argued that an alternative statistical analysis, such as the proportional-odds generalized estimating equation, is more suitable for longitudinal polytomous data³⁴.

Nature and mechanisms of pain after laparoscopy

Nature of pain

Pain is a subjective sensation, and its measurement and analysis are difficult. Pain is not only a sensory stimulus, but has motivational and affective components, and is experienced in the context of cultural learning, previous experience, anxiety and depression³⁵. Cultural factors affect the duration of pain and time to return to work after LC³⁶. Although LC can be done safely and successfully as a day-only procedure^{37,38}, the majority of patients still stay overnight³⁹. The individual dose of opiate analgesia required for postoperative analgesia varies significantly²⁸, with 10 per cent of patients reporting no significant pain after LC^{3,14,28,40}.

Ure *et al.*²⁸ assessed pain in 382 patients after the procedure. No analgesia was required by 26 per cent of patients and narcotic analgesia was required by 32 per cent. The site of most severe pain was in the right upper quadrant and port wounds during the first 24 h. The port-site wounds remained the most painful region on the first day after operation. This contrasts with the report of Joris *et al.*⁴¹ who differentiated pain into three components: visceral, abdominal wall, and referred to the shoulder. They found that pain was worst in the first 24 h after operation with visceral pain being worse than abdominal wall pain. A second peak of pain occurred in some patients in the shoulder tip on the second day after operation. A similar pattern was noted in the control group of a trial that assessed the use of postoperative drains³⁴. The incidence of shoulder tip pain after LC is usually reported to be 30–40 per cent⁴², although rates vary from 12 per cent³² to 80 per cent⁴⁰ in the papers reviewed for this study. Shoulder tip pain occurs after open surgery; one study comparing small-incision cholecystectomy with LC noted respective incidences of 13 and 23 per cent¹. Pain may also occur around the rib cage and back⁴².

Women report more pain than men, and postoperative pain correlates with preoperative pain levels²⁸. Jess *et al.*⁴³ assessed whether postoperative pain and recovery were related to patient behaviour. Recovery in the immediate postoperative period and pain at 1 year did not correlate with 'psychic vulnerability' or neuroticism scores; early postoperative pain scores were not assessed.

Mechanisms of pain

Factors that may influence the degree of pain after laparoscopic procedures include the volume of residual gas⁴⁴, the type of gas used for pneumoperitoneum⁴⁵, the pressure created by the pneumoperitoneum^{22,46} and the

temperature of insufflated gas^{47,48}. The length of the operation and volume of insufflated gas may also be related to postoperative pain, but these factors may correlate with each other⁴⁷ and not all trials examining the duration of pneumoperitoneum and postoperative pain have demonstrated a relationship^{41,49}. It seems that the total volume of carbon dioxide may be a more important factor than the duration of exposure. A recent trial suggests that the rate of insufflation of carbon dioxide also influences the incidence of postoperative pain, with lower rates of insufflation resulting in lower rates of shoulder tip pain⁵⁰.

Jackson *et al.*⁴⁴ measured the volume of the residual gas bubble after gynaecological procedures from a plain abdominal radiograph on the afternoon of surgery. They found that the amount of residual gas correlated with postoperative pain. This finding⁴⁴ differs from that of a study in which serial abdominal radiographs were performed⁵¹; this trial (showing that the mean duration of pneumoperitoneum after laparoscopic general surgical procedures is 2.6 days⁵¹) found no correlation between the duration or extent of pneumoperitoneum and pain. Interestingly, bile spillage from the gallbladder during LC was shown to be associated with more rapid resolution of the pneumoperitoneum⁵¹. This might possibly be related to subsequent lavage, with displacement of subphrenic carbon dioxide. Bile spillage is not associated with increased pain or slower postoperative recovery^{28,52}.

It is unclear whether there is increased pain associated with LC for acute cholecystitis. Theoretically the pre-operative inflammation may sensitize the central nervous system, resulting in worse postoperative pain⁵³. Although there is little clinical evidence to support this notion, it should be considered when evaluating postoperative pain in trials. Almost all trials presented in the present series have specified that only elective patients were used as subjects. The use of suxamethonium for induction of anaesthesia is another variable that should be standardized because of its potential side-effect of muscle pain⁶.

The exact mechanism of pain after laparoscopy has yet to be clarified. Proposed mechanisms include diaphragmatic stretching²², with phrenic nerve neuropraxia causing shoulder tip pain⁷. The short duration of the pain and the fact that the diaphragm is elevated by the pneumoperitoneum⁵⁴ indicate that it is unlikely to result from mechanical injury to the main phrenic nerve. It is possible that subdiaphragmatic fibres are stretched by the increased concavity of the diaphragm induced by the pneumoperitoneum. It is also suggested that the loss of visceral surface tension after creation of pneumoperitoneum results in increased weight on the diaphragmatic attachments of the liver and hence shoulder tip pain^{14,55}. However, Schoeffler *et al.*⁶ claim that more severe pain is noted in the left

shoulder tip owing to protection of the right diaphragm by the liver.

Neuropathic pain may be elicited by many other stimuli, including chemical irritation, ischaemia and compression⁵⁶. Attempts to ameliorate shoulder tip pain by gas aspiration³⁴ or local anaesthetic to the diaphragm^{15,16,31} are only moderately successful. Phrenic nerve block after the onset of anaesthesia significantly reduces the incidence of shoulder tip pain after operation⁵⁷.

The means by which pneumoperitoneum causes pain may be related to trauma. Peritoneal biopsies taken after laparoscopy show peritoneal inflammation, and capillary and neuronal rupture⁵⁸, and cytological examination shows granulocyte infiltration⁵⁹. A study examining the effects of laparoscopy with carbon dioxide on the free radical scavenger system found that the decrease in free radical scavengers in peritoneal biopsies correlates strongly with the exposure to carbon dioxide and the duration of the procedure⁶⁰. This contrasts with the minimal changes noted with superoxide anion release from macrophages after carbon dioxide pneumoperitoneum compared with exposure of the peritoneal cavity to air⁶¹. However, this animal study is unlikely to apply to operative laparoscopic procedures as the duration of pneumoperitoneum was only 60 s⁶¹. Another mechanism may be the formation of intraperitoneal carbonic acid from carbon dioxide^{59,62}. Localized peritoneal acidosis is demonstrable in a porcine model with carbon dioxide, but not with air, pneumoperitoneum; the degree of acidosis is related to the duration of pneumoperitoneum and intra-abdominal pressure⁵⁹. Intraperitoneal acidosis has also been documented in humans after carbon dioxide pneumoperitoneum⁶². Interestingly, acidosis was also found in a small number of patients with argon pneumoperitoneum⁶² which suggests that the acidosis may arise from local ischaemia. The benefit of saline may be in dilution of acid rather than restoration of visceral surface tension, as proposed by Tsimoyiannis *et al.*¹⁴, although normal saline is itself acidic. As well as local acidosis, it is hypothesized that systemic hypercarbia may cause sympathetic nervous system excitation, resulting in amplification of the local tissue inflammatory response⁶³. Splanchnic mucosal ischaemia is seen after pneumoperitoneum, even in healthy patients⁶⁴, and is another potential mechanism of postoperative pain.

The gynaecological literature suggests that the type of intra-abdominal procedure influences the degree of pain. Patients have more pain after laparoscopic sterilization than after diagnostic laparoscopy, despite the duration of tubal ligation being less than that of diagnostic laparoscopy⁶⁵. The method of sterilization also affects pain levels^{5,65}. It is uncertain whether such a difference also occurs between different general surgical operations³¹.

Thus the origin of pain after LC is multifactorial, with pain arising from the incision sites, the pneumoperitoneum and the cholecystectomy. It is likely that combined analgesic regimens addressing different mechanisms of pain will be the most useful in combating this postoperative problem.

Trials assessing methods of reducing pain after laparoscopic cholecystectomy

Non-steroidal anti-inflammatory drugs

Table 1 details trials assessing the use of NSAIDs. These trials, using a variety of agents, were all able to demonstrate a statistically significant reduction in some aspect of postoperative pain. This reduction was usually short lived and was confined to the first 24 h after operation. In the setting of outpatient LC, patients given NSAIDs combined with pre-emptive pethidine and wound local anaesthetic were discharged from hospital earlier than those given saline in one study⁶⁸. The major detectable benefit of NSAIDs appears to be as opiate-sparing agents. However, this does not uniformly result in a reduction in postoperative nausea and vomiting or sedation^{21,66,67}. A study by Forse *et al.*²⁵ demonstrated reduced postoperative nausea, but only in the recovery unit.

The best time to administer the NSAID may depend on its half-life²¹. One study compared pre-emptive *versus*

intraoperative ketorolac administration and found no difference in postoperative pain between the two groups²⁰. Trials evaluating NSAIDs will often exclude a large number of patients because of age, renal, cardiac, haematopoietic or hepatic impairment, a history of asthma, gastrointestinal bleeding or peptic ulcer disease, or use of diuretics or angiotensin converting enzyme inhibitors²¹. Because of reduced renal blood flow during pneumoperitoneum⁷¹, care may be required if NSAIDs are to be used. Ketorolac has been associated with the development of acute renal failure after surgery, although the risk is low⁷². It should be noted that since the time of the trials listed, the recommended dose of ketorolac has been reduced⁷³. Dipyrrone is not available in many countries owing to bone marrow suppression⁷³. None of the trials reports problems with postoperative bleeding.

Intraperitoneal local anaesthetic

Table 2 details trials assessing the use of intraperitoneal local anaesthetic, usually bupivacaine. The results of these studies have been conflicting. Eight of the 13 trials listed demonstrated some benefit in terms of pain reduction, although the magnitude of this reduction and the duration of effect were limited. No benefit was shown with respect to earlier discharge or earlier return to normal activity. It has been suggested that the poor results for overall pain reduction with intraperitoneal local anaesthesia after LC,

Table 1 Randomized controlled trials assessing the role of non-steroidal anti-inflammatory drugs

Reference	Year	n	Timing*	NSAID	Dose	Route	Control	Results
Wilson <i>et al.</i> ⁶⁶	1994	49	Before	Diclofenac	75 mg	i.m.	Saline	Pain significantly less at 4 h
Liu <i>et al.</i> ⁶⁷	1993	60	Before, during and after	Ketorolac	30–60 mg/kg	i.v.	Saline	Less requirement for fentanyl to 16 h
Michaloliakou <i>et al.</i> ⁶⁸	1996	49	Before	Ketorolac (+ pre-emptive pethidine and wound LA)	0.5 mg/kg	i.v.	Saline	Earlier discharge, reduced pain to 48 h
Munro <i>et al.</i> ²¹	1998	37	After	Tenoxicam	40 mg	i.v.	Saline	Less morphine required at 6 and 12 h but not at 24 h
Lane <i>et al.</i> ²⁰	1996	125	Before or during	Ketorolac	60 mg	i.m.	Pethidine or saline	Ketorolac better than pethidine and control
Forse <i>et al.</i> ²⁵	1996	52	Before	Ketorolac Indomethacin	30 mg 100 mg	i.m. p.r.	Saline	No difference between NSAIDs; reduced pain, less opiate and less nausea than control
Steffen <i>et al.</i> ⁶⁹	1997	40	Before and after	Dipyrrone	1000 mg	i.v.	Saline	Less pain and narcotic use to 24 h
Fredman <i>et al.</i> ⁷⁰	1995	60	During	Ketorolac Diclofenac	60 mg 75 mg	i.m. i.m.	Saline	No difference between NSAIDs; reduced pain and less opiate than control

*Before establishment of, during or after pneumoperitoneum NSAID, non-steroidal anti-inflammatory drug, LA, local anaesthetic; i.m., intramuscular; i.v., intravenous; p.r., rectal

Table 2 Trials of intraperitoneal local anaesthetic

Reference	Year	n	Timing*	Local anaesthetic	Concentration (%)	Dose	Volume (ml)	Control	Outcome
Pasqualucci <i>et al.</i> ⁷⁴	1994	42	Before and/or after	Bupivacaine + adrenaline	0.5	100–200 mg	20–40	Saline	Less pain in group receiving 40 ml bupivacaine
Pasqualucci <i>et al.</i> ¹⁶	1996	109	Before and/or after	Bupivacaine + adrenaline	0.5	100 mg	20–40	Saline	Less pain to 24 h for pre-emptive bupivacaine
Szem <i>et al.</i> ⁷⁵	1996	55	Before	Bupivacaine	0.1	100 mg	100	Saline	Modest reduction at 6 h only
Mraovic <i>et al.</i> ⁷⁶	1997	80	Before and after	Bupivacaine	0.5	150 mg	30	Saline	Significant difference to 8 h; lower analgesic consumption
Rademaker <i>et al.</i> ⁷⁷	1994	45	After	Bupivacaine Lignocaine	0.25 0.5	50 mg	20 20	Saline	Not effective
Scheinin <i>et al.</i> ⁷⁸	1995	60	After	Bupivacaine + adrenaline	0.15	150 mg	100	Saline	Not effective
Fuhrer <i>et al.</i> ⁷⁹	1996	24	After	Bupivacaine	0.375	2.25 mg/kg	42†	Saline	Not effective
Schulte-Steinberg <i>et al.</i> ⁸⁰	1995	110	After	Bupivacaine	0.25	50 mg	20	Saline or morphine	Not effective
Joris <i>et al.</i> ⁴¹	1995	40	After	Bupivacaine + adrenaline	0.125	100 mg	80	Saline	Not effective
Chundrigar <i>et al.</i> ³²	1993	58	After	Bupivacaine	0.25	50 mg	20	Saline	Less pain at 1 and 2 h only
Cunniffe <i>et al.</i> ³¹	1998	63	After	Bupivacaine	0.01	50 mg	500	Saline	Reduced shoulder tip pain to 24 h
Tsimoyiannis <i>et al.</i> ¹³	1998	300	After	Bupivacaine	0.25	1.5 mg/kg	25†	Saline or nothing	Effective, but saline more effective
Weber <i>et al.</i> ¹⁵	1997	150	After	Bupivacaine	0.5	50 mg	10	Saline or nothing	Effective

*Related to dissection, †approximate volume

compared with those in the available gynaecological literature^{5,81}, are due to visceral and parietal pain being more severe than shoulder tip pain⁴¹ after LC. If reduction of shoulder tip pain only is assessed, then benefit may be shown³¹ whereas overall pain may not be affected.

The dose of bupivacaine administered varies considerably between trials, ranging from 50 to 200 mg and concentrations vary between 0.01 and 0.5 per cent. Although no clinical toxicity has been reported at the higher doses, toxic levels were noted in one series in which patients received 150 mg, with serum levels monitored after operation⁷⁹. The peak serum level occurs 20–30 min after application of bupivacaine and the addition of adrenaline to the solution lowers peak plasma levels⁷⁸.

The bupivacaine solution is usually instilled through a laparoscopic port with the aid of a cannula or irrigator. Some authors have used a special low-pressure spraying device⁸⁰. The use of a subphrenic catheter, retained after operation for injection of bupivacaine and prilocaine, has been described⁸². The site of administration of bupivacaine varies and it is suggested that application to the right diaphragm is inadequate⁸³. Trials showing a benefit claim that application to both left and right sides of the

diaphragm³¹ and to the gallbladder bed⁷⁶ is important to maximize pain reduction. The position of the patient during instillation of the solution has differed, with some authors making no mention of changing position from reverse Trendelenburg⁴¹, others laying the patient supine⁷⁷, and others requiring the patient to be in the Trendelenburg position for 20 min⁷⁸. The timing of administration of the local anaesthetic solution has also varied. Pasqualucci *et al.*¹⁶ suggest that bupivacaine applied before dissection is better than application at the end of the procedure. Another trial, by Mraovic *et al.*⁷⁶, claims benefit from administration before dissection, although a direct comparison between preoperative and postoperative bupivacaine was not made. All four trials administering 'pre-emptive' analgesia demonstrated benefit in terms of pain reduction, whereas four of nine trials administering bupivacaine at the completion of the procedure showed some benefit. An editorial recommending routine use of intraperitoneal bupivacaine before dissection has been published⁸⁴.

There is still no conclusive evidence of the value of pre-emptive analgesia for any procedure in the clinical setting⁵³. The aim of early administration of analgesics is to prevent the establishment of central sensitization to noxious stimuli;

application of bupivacaine after creating the pneumoperitoneum would not pre-empt the trauma that creating a pneumoperitoneum might cause. Pasqualucci *et al.*¹⁶ suggest that instillation of bupivacaine before dissection has both short-term local anaesthetic effects with some reduction of shoulder tip pain, and some ability to suppress the central appreciation of pain. Although they did not evaluate different components of pain, they propose that visceral pain, secondary to dissection of the gallbladder, may be improved by the early administration of local anaesthetic.

Finally, a trial comparing bupivacaine in a large volume of saline to saline alone found that both provided improved analgesia, of equivalent magnitude¹³. A small volume of bupivacaine also reduced pain in this study but to a lesser degree than saline alone. Thus, the volume of local anaesthetic used may provide part of its analgesic benefit, although most trials showing benefit used a small volume of both bupivacaine and saline.

Wound local anaesthetic

Table 3 details trials assessing the use of local anaesthetic applied to the wound. The conclusion from these studies is that wound local anaesthetic provides some benefit in pain reduction, which is again short lived. Pre-emptive injection does not appear as effective as postoperative injection⁸⁶. Infiltration around the peritoneum and subcutaneously is better than subcutaneous infiltration alone⁸⁵. The study by Ure *et al.*²³, showing no benefit, had a trend towards less pain in the wound infiltration group. Their sample size calculation was designed to detect a difference in VAS scores of 15 points on a 100-point scale. A difference of up to 9 points was demonstrated, but they argue (correctly) that this is not a clinically relevant difference.

Intraperitoneal saline

Two interesting studies^{13,14} from the same research group compare several interventions including the effect of intraperitoneal saline on postoperative pain. The first trial¹⁴

had five arms of 60 patients. These arms were standard LC, LC with a suction drain, LC with instillation and aspiration of saline, LC with instillation of saline that was left intraperitoneally, and LC with instillation and aspiration of saline and a suction drain. The volume of saline used was between 25 and 30 ml/kg and was the volume required to cover the surface of the liver. Despite some methodological concerns regarding randomization, the results appear convincing. The control group reported significant pain in 90 per cent of cases; the groups receiving saline reported significant pain in only 22–30 per cent of cases. The second trial¹³ had six arms of 50 patients (it is not clear whether some of the same patients were used for both studies). This trial compared standard LC with LC with saline and a drain, LC with intraperitoneal bupivacaine, LC with intraperitoneal bupivacaine and a drain, LC with intraperitoneal bupivacaine and saline, and LC with bupivacaine, saline and a drain. Ten per cent of patients in the standard LC group required no analgesia compared with 40 per cent of patients receiving bupivacaine and 80–84 per cent of patients having saline with or without bupivacaine. The conclusion offered, that normal saline plus bupivacaine is better than saline alone if a drain is not used, is not substantiated by the data. However, the finding that a large volume of saline, whether instilled and left, or aspirated, significantly reduces pain is promising and suggests a simple way to reduce postoperative pain.

Only one other trial has used a considerable volume of saline³¹ but it had no non-saline controls. It found that the addition of bupivacaine reduced shoulder tip pain to a greater extent than 500 ml saline alone. Total abdominal pain was not assessed. This volume of saline is considerably less than the amount used in the trials by Tsimoyiannis *et al.*^{13,14}, in which over 2 litres was frequently used.

Removal of insufflation gas

Table 4 details trials assessing the benefit of evacuating the gas used for pneumoperitoneum. Only the trial by Jorgensen *et al.*³⁴ blinded the pain scorers and patients to

Table 3 Trials of wound local anaesthetic

Reference	Year	n	Timing*	Anaesthetic	Volume	Control	Outcome
Alexander <i>et al.</i> ⁸⁵	1996	80	After	Bupivacaine 0.25%	40 ml s.c. and peritoneal	Bupivacaine 0.5% 20 ml s.c.	Less pain in patients with peritoneal injection, at 6 and 18 h
Sarac <i>et al.</i> ⁸⁶	1996	70	Before or after	Bupivacaine 0.5%	14 ml	Saline	Reduced pain and analgesia, up to 4 h, postoperative LA better than preoperative
Ure <i>et al.</i> ²³	1993	50	Before	Bupivacaine 0.5%	32 ml	Saline	No benefit

*Related to dissection. LA, local anaesthetic, s.c., subcutaneous

Table 4 Trials of removal of insufflation gas

Reference	Year	n	Intervention	Control	Outcome
Jorgensen <i>et al.</i> ³⁴	1995	41	Right subphrenic closed suction drain	Drain, no suction	Less shoulder tip pain to day 3
Hawasli and Brown ¹⁹	1994	100	Drain through epigastric port	No drain, not blinded	A drain delayed discharge, no reduction in pain
Tsimoyiannis <i>et al.</i> ¹⁴	1998	120	Subhepatic closed suction drain	No drain, not blinded	No reduction in pain
Fredman <i>et al.</i> ¹⁷	1994	33	Active aspiration of gas	Non-active aspiration	Less analgesic demand in first hour

Table 5 Trials of insufflated gases

Reference	Year	n	Intervention	Control	Outcome
Koivusalo <i>et al.</i> ¹⁸	1996	26	Gasless, abdominal wall lift	Standard CO ₂ , pressure 12–15 mmHg	Less shoulder pain with gasless LC
Aitola <i>et al.</i> ⁴⁵	1998	40	N ₂ O	CO ₂	Less pain at 1, 6 and 24 h
Mouton <i>et al.</i> ⁴⁸	1998	32	Heated and humidified CO ₂	CO ₂	Less pain days 1 and 10, earlier return to activity
Unbehaun <i>et al.</i> ⁴⁶	1995	71	Pressure 8–10 mmHg	Pressure 14–16 mmHg	Less analgesic requirement day 1
Wallace <i>et al.</i> ²²	1997	40	Pressure 7.5 mmHg	Pressure 15 mmHg	Less pain to 6 days
Berberoglu <i>et al.</i> ⁵⁰	1998	76	Flow 2.5 l/min	Flow 7.5 l/min	Less shoulder pain with low flow rate at day 3

LC, laparoscopic cholecystectomy

the presence of a functioning drain. A reduction in shoulder tip pain was achieved, although the impact on overall pain was minimal. The other trials have shown no benefit from drainage. The gynaecological literature suggests that a gas drain is beneficial⁸⁷. The reduced visceral pain and correspondingly worse shoulder tip pain with gynaecological procedures may mean that reduction of shoulder tip pain provides a greater relative benefit for gynaecological procedures. Attempts to aspirate gas are usually unsuccessful⁸⁸. 'Active' aspiration lessened analgesic demand in only the first hour after operation¹⁷.

Characteristics of insufflation gas

Table 5 details trials assessing characteristics of the gas used for peritoneal insufflation. These have shown positive results in terms of reduction of pain after LC, although randomized trials involving patients having gynaecological procedures have not always supported these conclusions. Despite a longer operating time, the use of a mechanical lifting device rather than carbon dioxide pneumoperitoneum resulted in less shoulder tip pain, reduced drowsiness and earlier mobilization¹⁸. There was no difference in the total amount of pain or analgesic requirements between the two groups; long-term pain was not evaluated. The authors comment that the patients in the mechanical lift arm experienced pain that was unpleasant and 'like tenderness after a hard

muscle work out' the day after operation. Two gynaecological randomized trials comparing a mechanical lifting device with standard carbon dioxide pneumoperitoneum found no reduction in pain⁸⁹ but increased technical difficulty with the use of the lifting device⁹⁰.

The use of nitrous oxide rather than carbon dioxide for LC reduces pain scores at 1, 6 and 23–24 h, but not in intervening time periods⁴⁵. There has been concern about the possibility of combustion with the use of nitrous oxide, but the risk appears theoretical⁹¹. The gynaecological literature also supports reduced pain with nitrous oxide use^{92,93}. Argon and helium have also been evaluated as gases for pneumoperitoneum⁹⁴, with the focus being on their effects on haemodynamic and respiratory function⁹⁵, and tumour implantation⁹⁶. One German trial assessed the effect of argon on postoperative pain in eight patients undergoing laparoscopic procedures, but lacked the power to demonstrate any difference⁶².

Heated gas appears to have the ability to produce a prolonged reduction in pain after both gynaecological procedures^{47,97} and LC⁴⁸. The trial assessing pain after LC, using heated and humidified gas, also showed earlier return to 'normal' activities⁴⁸. At present there is no clinical evidence to suggest that heated and humidified gas is superior to heated gas alone in its association with pain reduction. Theoretically⁹⁸, and in animal experiments⁹⁹, humidified gas results in less heat loss, but the mechanism by which heated gas results in pain reduction is unknown.

The use of warm gas may result in a reduction in carbon dioxide volume^{97,100}.

The use of low-pressure insufflation compared with standard insufflation also (statistically) improves pain scores up to 6 days and enables earlier hospital discharge. It does however, make introduction of ports difficult and reduces visibility. Five of 20 patients in one study required conversion to higher-pressure insufflation to complete the procedure²². The data were analysed on an intention-to-treat basis. The volume of carbon dioxide used in each group was not reported and it is possible that carbon dioxide volume is a confounding factor in the results. A German study also addressed this issue, comparing pressures of 8–10 mmHg with 14–16 mmHg, and found a significant reduction in analgesia requirement but no benefit in functional outcome⁴⁶. It assessed carbon dioxide volume and found a reduction in gas volume with low-pressure pneumoperitoneum. However, analysis in this study is difficult because of a large number of exclusions in the low-pressure group and the division of patients into six subgroups, based on the ease of operation. In addition, different insufflators were used between groups and a higher rate of insufflation was used for the low-pressure group. High rates of insufflation may be associated with more postoperative pain⁵⁰. Comparison of insufflation rates of 2.5 and 7.5 l/min demonstrated less shoulder tip pain in the group with a low insufflation rate. This trial was multi-centred and the baseline equivalence of the experimental groups was not reported. The volume of carbon dioxide used and the mean pressure of the pneumoperitoneum were not recorded. The pneumoperitoneum pressure limit was set between 12 and 15 mmHg. It is possible that the group with a low flow rate had a pressure considerably lower than the set pressure for much of the procedure if a gas leak was present, or when suction was used.

Size and number of ports

There has been only one randomized controlled trial evaluating the effect of an epigastric 5- or 10-mm port on postoperative pain¹², with no difference found. Numerous other trials have described the use of three- or two-port LC or 'needleoscopic' cholecystectomy¹⁰¹, but randomized data are lacking. Pain was measured as a secondary outcome in a study comparing the effects of undergoing LC by the 'French' or the 'American' technique on respiratory function²⁴. Pain scores at 48 h showed that patients having the 'French' procedure experienced less pain. A possible reason for this is the different placement of the ports²⁴, although the type of operation was not concealed from patients or assessors.

Anaesthetic intervention

Two studies have assessed the use of epidural analgesia and demonstrate a reduction in early postoperative pain^{26,102}. However, an epidural seems unduly invasive and unnecessary in the context of minimally invasive surgery. The rationale for its use is its ability to provide pre-emptive central blockade and so minimize narcotic-related side-effects⁶³.

In a single-blind trial a right phrenic nerve block with 10 ml 1 per cent mepivacaine was performed immediately after intubation and before pneumoperitoneum⁵⁷. The incidence of shoulder tip pain was 5 per cent in patients receiving such a phrenic nerve block and 38 per cent in controls. This did not result in a significant difference in analgesia requirements.

When used for maintenance of anaesthesia, propofol and opiate supplements (total intravenous anaesthesia) were associated with less pain and nausea than desflurane in the recovery unit, but this difference disappeared at 24 h¹⁰³. This finding is not supported in another trial comparing the use of intravenous anaesthesia (propofol or methohexitone) with isoflurane. There was no significant difference in pain but greater nausea with the intravenous agents¹⁰⁴.

Finally, one study examining intraperitoneal bupivacaine also assessed 'interpleural' bupivacaine and morphine for postoperative analgesia⁸⁰; 'interpleural' bupivacaine was successful in pain reduction for up to 6 h, but 'interpleural' morphine was not.

Conclusion

LC lends itself readily to trials examining methods of reducing postoperative pain. It is a procedure that can be standardized with control of most intraoperative variables. It is also a procedure that is performed frequently, so that data accrue quickly. It is regrettable that many of the published trials lack statistical rigour and fail to assess so-called 'soft data', such as quality of life and fatigue. A formal assessment of the quality of the trials in this review was not made, but obvious deficiencies have been detailed.

From the reviewed literature it is concluded that NSAIDs, intraperitoneal bupivacaine, saline and wound local anaesthetic are able to reduce pain after LC. None of these studies has demonstrated a prolonged reduction in pain or improved functional outcome. Limiting the amount of opiate analgesia during the first 24 h is clinically irrelevant if the hospital derives no benefit from earlier discharge and the patient derives no benefit through more rapid recovery. The ability to limit opiate use in the first 24 h does not appear to translate into less sedation or nausea and vomiting for patients in hospital. Heated and humidified gas

and lower pressure of gas insufflation are two measures that have been demonstrated in single trials to provide improved outcome after 48 h. One trial showed that the use of multimodal analgesia permits earlier discharge and more patients to be managed as outpatients.

As the pain from LC is multifactorial, it is likely that several methods of analgesia combined will best reduce postoperative pain. There is room for confirmation of the findings of trials involving the role of intraperitoneal local anaesthetic before dissection and the role of intraperitoneal saline in the reduction of pain. Improved understanding of the pathogenesis of postoperative pain may enable novel approaches to analgesia. The demonstration of free radical depletion after carbon dioxide pneumoperitoneum may indicate a role for antioxidant drugs. Improved and selective anti-inflammatory drugs may provide a better safety profile. Finally, the development of sturdier, smaller instruments may reduce wound pain, although the size of incision needed to extract the gallbladder often proves a limiting factor.

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Randomized clinical trial of granisetron, droperidol and metoclopramide for the treatment of nausea and vomiting after laparoscopic cholecystectomy

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Background: Patients undergoing laparoscopic cholecystectomy (LC) may be especially at risk of experiencing postoperative nausea and vomiting (PONV). This study was undertaken to evaluate the efficacy of granisetron, droperidol and metoclopramide for the treatment of PONV after LC.

Methods: After experiencing PONV during the first 3 h after recovery from anaesthesia, 120 patients (78 women) received, in a randomized double-blind manner, granisetron 40 µg/kg, droperidol 20 µg/kg or metoclopramide 0.2 mg/kg ($n = 40$ per group) intravenously. Patients were then observed for 24 h after administration of the study drug.

Results: Complete control of established PONV, defined as no emetic symptoms and no need for another rescue antiemetic medication, was achieved in 88 per cent of patients with granisetron, 60 per cent with droperidol and 55 per cent with metoclopramide ($P < 0.05$). No clinically adverse events were observed in any of the groups.

Conclusion: A high dose of granisetron (40 µg/kg) was more effective than droperidol 20 µg/kg or metoclopramide 0.2 mg/kg for the treatment of established PONV after LC.

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Introduction

Postoperative nausea and vomiting (PONV) are distressing and frequent adverse events after general anaesthesia and surgery¹. The incidence of PONV has been shown to be 25–42 per cent with no antiemetic treatment in patients undergoing laparoscopic cholecystectomy (LC)^{2,3}. Granisetron, like ondansetron, is a selective antagonist of the 5-hydroxytryptamine type 3 (5-HT₃) receptor, and is effective for the treatment of emesis in patients receiving cytotoxic drugs⁴. Granisetron is more potent and is longer acting against emesis associated with chemotherapy than ondansetron⁵. It was demonstrated recently that prophylactic therapy with granisetron is effective for preventing PONV after LC⁶. However, there have been no studies to evaluate the efficacy of granisetron for the control of established PONV in patients undergoing LC. This study was undertaken, in a randomized double-blind manner, to compare the efficacy of granisetron with that of other commonly used and well established antiemetics, droperidol and metoclopramide, for the treatment of established PONV after LC.

Patients and methods

Institutional ethics committee approval and informed consent from each patient were obtained. Eligible patients were those experiencing nausea lasting more than 10 min and/or emesis (vomiting, retching) within 3 h after recovery from general anaesthesia. There were 120 patients (78 women) aged 23–63 years, who were classified as American Society of Anesthesiologists grade I or II. Patients who had gastrointestinal disease, those who had a history of motion sickness and/or previous PONV, those who were pregnant or menstruating, or those who had taken antiemetics within 24 h before operation were excluded from the study.

No patient received preanaesthetic medication. Anaesthesia was induced with intravenous administration of thiopentone 5 mg/kg and fentanyl 2 µg/kg, and intravenous vecuronium 0.2 mg/kg was used to facilitate tracheal intubation. After tracheal intubation, anaesthesia was maintained with isoflurane 1.0–3.0 per cent (inspired concentration) and nitrous oxide (66 per cent in oxygen). Ventilation was mechanically controlled and was adjusted to keep an end-tidal concentration of carbon dioxide

between 4.6 and 5.2 kPa throughout the surgical procedure, as measured by an anaesthetic/respiratory analyser (Ultima; Datex, Helsinki, Finland). Muscle relaxation was achieved with vecuronium as required. A nasogastric tube was inserted, and suction was applied to empty the stomach of air and other contents. Before tracheal extubation, the nasogastric tube was again suctioned and then removed. At the end of surgery, atropine 0.02 mg/kg and neostigmine 0.04 mg/kg were administered for reversal of muscle relaxation, and the trachea was extubated. Rectal temperature was monitored and maintained at $37 \pm 1^\circ\text{C}$ using a warming pad. After operation, all patients were admitted to the hospital for a couple of days. Patients were not allowed to have solid food within 24 h after operation. Clear liquids were not permitted up to 6 h after surgery. Postoperative analgesia was provided by indomethacin 50 mg rectally for moderate pain and pentazocine 15 mg intramuscularly for severe pain.

Immediately after experiencing nausea lasting more than 10 min and/or emesis (vomiting, retching) during the first 3 h after anaesthesia in the postanesthetic care unit, patients received, in a randomized double-blind manner, granisetron 40 µg/kg, droperidol 20 µg/kg or metoclopramide 0.2 mg/kg intravenously. A randomization list was generated and identical syringes containing each drug were prepared by personnel not involved in this study, according to the list. Patients were then observed for 24 h after administration of the study drug. All episodes of emetic symptoms (nausea, retching, vomiting) were recorded by a research nurse blinded to which treatment each patient had received. Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; retching was defined as the laboured spasmodic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents; and vomiting was defined as the forceful expulsion of gastric contents from the mouth¹. A complete control of established PONV was defined as no emetic symptoms and no need for another rescue antiemetic medication. If two or more episodes of emesis occurred within 24 h after administration of the study drug, another rescue antiemetic (e.g. domperidone rectally) was given.

At the end of the observation period, each patient evaluated the severity of nausea and satisfaction resulting from the study drug, and a nurse evaluated the patient's level of sedation. The evaluations were performed on a linear numerical scale ranging from 0 (no nausea; complete satisfaction; no sedation) to 10 (severe nausea; complete dissatisfaction; extreme sedation). Details of any other adverse events throughout the study were recorded by the nurse, who interviewed each patient and also recorded spontaneous complaints.

Statistical analysis

Patient demographic data were analysed using analysis of variance with Bonferroni's correction for multiple comparison and χ^2 test. The number of patients with complete control of established PONV (no emesis, no rescue), nausea, retching, vomiting and requiring another rescue antiemetic, and the incidence of adverse events were compared with Fisher's exact probability test. The severity of nausea, patient satisfaction and degree of sedation assessed by a research nurse were analysed with the Mann-Whitney *U* test. $P < 0.05$ was considered significant. Power analysis was used to determine the number of patients in the study based on the assumption that (1) complete control of PONV would be achieved in 60 per cent of patients receiving droperidol or metoclopramide, (2) an improvement from 60 to 85 per cent was considered to be of clinical importance and (3) $\alpha = 0.05$ and a power $(1 - \beta)$ of 80 per cent. Based on these assumptions, 40 patients per group were required.

Results

The treatment groups were comparable with regard to patient demographics (*Table 1*).

Complete control of established PONV (no emesis, no rescue) for 24 h after administration of the study drug was achieved in 88 per cent of patients with granisetron, 60 per cent with droperidol and 55 per cent with metoclopramide. Granisetron achieved complete control in a significantly greater proportion of patients than either droperidol or metoclopramide ($P < 0.05$), while there was no significant difference between the droperidol and metoclopramide groups (*Table 2*).

The severity of nausea was less in patients who had received granisetron than in those who had received droperidol or metoclopramide ($P < 0.05$). Patients who had received granisetron were more satisfied than those who had received droperidol or metoclopramide ($P < 0.05$). However, there were no differences in the severity of nausea and satisfaction resulting from the study drug between the droperidol and metoclopramide groups. No difference in sedation was observed among the groups (*Table 2*).

The most frequently reported adverse events were headache and dizziness, which were not serious. No differences in the incidence of adverse effects were observed among the groups (*Table 3*). No extrapyramidal symptoms were observed in any of the groups.

Discussion

PONV is among the most common complications following anaesthesia and surgery, with a relatively high incidence

Table 1 Patient demographics

	Granisetron (n=40)	Droperidol (n=40)	Metoclopramide (n=40)
Age (years)*	47(8) (23–63)	46(8) (26–63)	46(9) (25–63)
Sex ratio (F/M)	27/13	26/14	25/15
Height (cm)†	157(7)	156(6)	155(6)
Weight (kg)†	56(7)	54(8)	54(6)
Last menstrual cycle (days)‡	16(3) (23‡)	16(3) (22‡)	16(3) (23‡)
Duration of operation (min)†	84(31)	84(28)	83(34)
Duration of anaesthesia (min)†	108(32)	106(30)	106(34)
Postoperative analgesia			
Indomethacin (n)	27	26	27
Pentazocine (n)	3	3	3

*Values are mean(s.d.) (range) or †mean(s.d.). ‡No. of patients who had experienced the menopause and were excluded

Table 2 Patients experiencing complete control of established postoperative nausea and vomiting, nausea, retching, vomiting, requiring another rescue antiemetic, severity of nausea, patient satisfaction and sedation assessed by a research nurse for 24 h after administration of antiemetic

	Granisetron (n=40)	Droperidol (n=40)	Metoclopramide (n=40)	P ₁	P ₂	P ₃
Complete control of established PONV*	35 (88)	24 (60)	22 (55)	0.005	0.001	0.411
Nausea*	3 (8)	9 (22)	10 (25)	0.057	0.033	0.5
Retching*	0 (0)	2 (5)	3 (8)	0.247	0.12	0.5
Vomiting*	2 (5)	7 (18)	8 (20)	0.077	0.043	0.5
Rescue*	0 (0)	7 (18)	8 (20)	0.006	0.003	0.5
Severity of nausea†	0 (0–5)	0 (0–10)	1 (0–10)	0.015	0.004	0.711
Patient satisfaction†	0 (0–5)	2 (0–10)	2 (0–10)	0.005	0.001	0.312
Sedation assessed by a research nurse†	0 (0–5)	0 (0–6)	0 (0–5)	0.726	0.856	0.862

*Values in parentheses are percentages; †values are median (range). PONV, postoperative nausea and vomiting (no emesis, no rescue) P₁, granisetron versus droperidol; P₂, granisetron versus metoclopramide, P₃, droperidol versus metoclopramide. Fisher's exact probability test or Mann-Whitney U test

after LC^{2,3}. The aetiology of PONV following LC is complex and is dependent on a variety of factors, including patient demographics, type of surgery, anaesthetic technique and postoperative care¹. Patient-related factors are age, sex, obesity, a history of motion sickness and/or previous PONV, and menstrual cycle. In this study, however, the treatment groups were comparable with regard to patient demographics, operative procedure, anaesthetic administered and analgesics used after operation. Therefore, the difference in control of established PONV (no emesis, no rescue) can be attributed to the study drug administered.

Granisetron has been reported to be effective for the treatment of emesis induced by cancer chemotherapy⁴ and is effective for preventing PONV in patients undergoing LC⁶. The precise mechanism by which granisetron prevents PONV remains unclear, but it has been suggested that it may act on sites containing 5-HT₃ receptors with demonstrated antiemetic effects⁷. However, the aetiology of

Table 3 Adverse events

	Granisetron (n=40)	Droperidol (n=40)	Metoclopramide (n=40)
Headache	3 (8)	3 (8)	2 (5)
Dizziness	2 (5)	2 (5)	2 (5)
Others*	1 (2)	1 (2)	1 (2)

Values in parentheses are percentages. *Constipation, muscle pain

PONV in patients undergoing LC is not identical to that in patients receiving cytotoxic drugs. Further studies are required to elucidate the mechanism of action of granisetron for the control of established PONV following LC.

The effective dose of granisetron is between 40 and 80 µg/kg for the treatment of cancer therapy-induced emesis⁸. It has recently been demonstrated that 40 µg/kg

is the minimum effective dose of granisetron for preventing PONV in patients undergoing LC⁹. As previously demonstrated in several reports^{10,11}, the dose of ondansetron, the 5-HT₃ receptor antagonist first described as an antiemetic, required for the prevention of PONV was comparable to that for the treatment of established PONV. Therefore, the same dose of granisetron (40 µg/kg) was chosen in this clinical trial. The doses of other antiemetics, droperidol and metoclopramide, were chosen from the results of several investigations of the prevention and treatment of PONV^{12,13}. Appropriate doses of these antiemetics, droperidol 20 µg/kg and metoclopramide 0.2 mg/kg, have been used for the control of PONV¹ and were also used in the present study.

In this study granisetron achieved complete control of established PONV (no emesis, no rescue) for 24 h in a greater proportion of patients than droperidol or metoclopramide ($P < 0.05$), but there was no difference between the droperidol and metoclopramide groups. These results suggest that the efficacy of granisetron is superior to that of droperidol or metoclopramide for the treatment of established PONV after LC.

Adverse events observed in this study were not serious. There were no differences among the treatment groups regarding the incidence of headache and dizziness, and the degree of sedation assessed by a research nurse. Extrapyramidal symptoms were not observed in any of the groups. Thus, the safety profiles of granisetron, droperidol and metoclopramide were similar.

In Japan, granisetron (US \$102.00 for 3 mg), like ondansetron (US \$103.00 for 3 mg), is more expensive than other antiemetics, droperidol (US \$1.80 for 1.25 mg) and metoclopramide (US \$0.60 for 10 mg). However, in this study granisetron was more effective than droperidol or metoclopramide for the treatment of established PONV after LC. In addition, patients who received granisetron were more satisfied than those who received droperidol or metoclopramide. The use of granisetron for reducing the incidence of established PONV may be justified by the incremental effectiveness (i.e. antiemetic efficacy).

In conclusion, a high dose of granisetron (40 µg/kg) was better than droperidol 20 µg/kg or metoclopramide 0.2 mg/kg for the control of established PONV in patients undergoing general anaesthesia for LC.

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Late results of a randomized clinical trial comparing total fundoplication *versus* calibration of the cardia with posterior gastropexy

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Background: The aim was to perform a prospective randomized study in patients with chronic gastro-oesophageal reflux treated either by total fundoplication or calibration of the cardia with posterior gastropexy. Late follow-up considered subjective and objective parameters, and related outcome to the presence of Barrett's oesophagus.

Methods: A total of 164 patients were randomized to fundoplication ($n = 76$) or calibration of the cardia ($n = 88$). They were evaluated by clinical questionnaire, upper gastrointestinal endoscopy with biopsies, oesophageal manometry and gastro-oesophageal reflux studies, including scintigraphy and 24-h oesophageal pH monitoring.

Results: There were no operative deaths. There was 95 per cent follow-up at a mean of 85 months. The mean recurrence rate for both operations was near 40 per cent at 10 years, but patients without Barrett's oesophagus had a recurrence rate after both operations of around 23 per cent compared with 83 per cent after 10 years for those with Barrett's oesophagus ($P < 0.0001$). Low-grade dysplasia developed in 13 per cent of the patients with Barrett's oesophagus. There were significant differences in all objective parameters in a comparison of patients with Visick I or II and those with Visick III or IV disease at the late assessment.

Conclusion: Both total fundoplication and calibration of the cardia with posterior gastropexy had similar subjective and objective late results. However, results were significantly worse in patients with Barrett's oesophagus.

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Introduction

Gastro-oesophageal reflux disease (GORD) is a chronic illness that becomes recurrent or progressive in 25 per cent of patients. Surgical treatment is the only effective cure at this stage^{1,2}. Comparison of medical and surgical treatment for GORD has demonstrated the superiority of surgery compared with H₂ blocking drugs^{3,4}, although no such comparisons have been made with proton pump inhibitors.

Several surgical techniques have been used for GORD, including Nissen total fundoplication (or its several variations) and the Hill–Larraín posterior gastropexy with calibration of the cardia^{5–16}. Prospective randomized studies comparing the late results of different surgical techniques are often flawed by the small number of patients included in the trial and short follow-up^{17–26}. The purpose of this prospective randomized study was to assess the late

subjective and objective results in a large number of patients submitted to two different antireflux procedures.

Patients and methods

Patients

This prospective trial started in January 1985 and ended in December 1997. Some 164 patients with chronic symptomatic gastro-oesophageal reflux of at least 3 years' duration were included; the mean duration of symptoms was 106 (range 36–360) months. There were 113 women (69 per cent) and 51 men (31 per cent) with a mean age of 44 (range 21–74) years. All patients gave their consent to be included in this protocol. Patients with complicated Barrett's oesophagus causing peptic ulcer, stricture, short oesophagus or dysplasia were excluded, but those with uncompli-

cated Barrett's oesophagus were randomized. Other exclusions were patients with a large, fixed intrathoracic hiatal hernia or paraoesophageal hernia, as well as those under 20 years of age. In 18 per cent of patients a previous cholecystectomy had been done and 32 per cent had associated gallstones. Duodenal ulcer was present in 6 per cent of the patients.

Symptomatic evaluation

A clinical questionnaire was given to each patient regarding the presence of heartburn, regurgitation, dysphagia, respiratory symptoms, epigastric pain and retrosternal pain. The severity of heartburn, regurgitation and dysphagia were classified in three categories (mild, moderate and severe) according to the criteria described by Zaninotto *et al.*²⁷.

Upper gastrointestinal endoscopy

This procedure was performed using a GIFXQ-20 endoscope (Olympus, Tokyo, Japan). The endoscopic aspect of the distal oesophagus was evaluated carefully and the Savary-Miller classification of oesophagitis was employed²⁸. Three groups of patients were defined according to the endoscopic findings:

- (1) Forty-four patients with GORD without endoscopic oesophagitis.
- (2) Eighty-one patients with erosive oesophagitis (presence of isolated or confluent erosions at the distal oesophagus).
- (3) Thirty-nine patients with uncomplicated long-segment Barrett's oesophagus. All had 3 cm or more of the distal oesophagus covered by specialized columnar epithelium. Biopsies taken from the oesophagus confirmed the presence of intestinal metaplasia in 28 patients. In 23 of these patients erosive oesophagitis was also present at the distal oesophageal mucosa, proximal to the squamocolumnar junction.

Manometric evaluation

Manometry was carried out after 12 h of fasting with the patient supine²⁹⁻³¹. The device consisted of four polyvinyl catheters bound together so that the 0.5-mm side holes were 3 cm apart (Synectics Medical, Stockholm, Sweden). Each catheter was perfused from a pneumohydraulic pump (Arndorfer Medical Specialties, Milwaukee, Wisconsin, USA) at a rate of 0.5 ml/min. Before each test, the system was calibrated so that sudden occlusion of the side hole produced an increase of 400 mmHg in 1 s. The end-expiratory fundic pressure was taken as zero reference.

Three manometric characteristics of the lower oesophageal sphincter (LOS) were determined^{27,31}: resting pressure, total length and abdominal length. The latter measurement was taken from the distal end of the sphincter up to the respiratory inversion point, which is the level at which the end-expiratory pressure changes from a positive to a negative deflection^{27,31}. In each patient three slow pull-throughs were obtained. The mean values were calculated from all measurements of the three catheters, giving 12 determinations in each patient. The amplitude of the distal oesophageal contractile waves was also determined. The protocol established that this test was performed before, 2-6 months after surgery and 5 years after operation, or if symptoms recurred. In 62 patients manometric evaluation was performed three times after surgery in order to evaluate late behaviour of the LOS.

Twenty-four-hour oesophageal pH study

This test has been performed since 1990. After 12 h of fasting the catheter was introduced through the nose and passed to the stomach (Digitrapper; Synectics Medical). It was then placed 5 cm above the LOS (manometry was always done first). A microcomputer analysed more than 20 000 determinations during 24 h^{32,33}. Of six different parameters that could be evaluated, the most useful was the total percentage of time in which the oesophageal pH remained below 4 (in normal subjects this occurs in less than 4 per cent of the time during 24 h). This test was performed before operation in the last 61 patients included in the study and then repeated 5 years after surgery in 46.

Scintigraphy

Determination of the magnitude of gastro-oesophageal reflux before surgery was performed employing ^{99m}Tc as described previously³⁴. This test was performed in 117 patients before 1990, and was positive in 107 (91 per cent).

Methods of randomization

Under general anaesthesia and after careful abdominal exploration, the surgeon decided whether the patient was suitable for randomization. Surgeons who participated in this trial had extensive previous experience in both antireflux surgical procedures. Randomization was performed by sealed envelope. At the beginning of this protocol, it was planned that this study should last 7 years (January 1985 to December 1991) and include 200 patients (100 of each operation). After 7 years, 188 patients (94 per cent) had been considered, but only 164 cases could be included. A total of 76 patients were randomized to

fundoplication and 88 to calibration of the cardia. Twelve patients were excluded during abdominal exploration owing to the presence of other surgical diseases not detected previously. Twelve additional patients refused to be included in the trial.

Surgical procedures

The patient was placed in a tilted position with the chest elevated relative to the feet. A careful dissection of the oesophagogastric junction with resection of the fat pad was performed, similar to that in highly selective vagotomy¹³⁻¹⁶. Three to four short gastric vessels were always divided. The posterior crus of the diaphragm was approximated with two non-absorbable silk stitches. For posterior gastropexy and calibration of the cardia, the procedure was performed by approximating the anterior portion of the gastro-oesophageal junction or cardia with its posterior equivalent from right to left in an 'adjusted' or calibrated long wrap, using four to five non-absorbable interrupted stitches. The last stitch was defined when a tense ring was created around a 30-Fr bougie. Two stitches of this calibration were then sutured to the distal segment of the crus (posterior gastropexy). This procedure is thought to work by regaining the normal tension of the sling fibres of the LOS and increasing the length of the abdominal portion of the sphincter by the posterior gastropexy.

For total Nissen fundoplication, a 4-cm long 'floppy' wrap was created, suturing the anterior and posterior walls of the gastric fundus after division of three to four short gastric vessels. A 360° wrap was constructed around the oesophagogastric junction in a 'floppy' fashion; late complications such as displacement or intussusception of the wrap were prevented by suturing both the proximal and distal stitches to the oesophageal wall. This procedure was designed to restore the normal manometric characteristics of the LOS.

Two sutures were always placed between the fundus and the anterior part of the diaphragm to avoid anterior paraoesophageal hernia which occurred in 5 per cent of the patients included in a previous protocol¹². A nasogastric tube was usually inserted for 24 h. Oral feeding restarted 2 days after surgery, and most patients were discharged from hospital after 5 days.

Definition of recurrence

The definition of recurrence and failure of the operation was based on two main findings:

- (1) Use of a modified Visick score at the late postoperative assessment³⁵ that included clinical evaluation of the presence of symptoms as follows: Visick I, no symp-

toms; Visick II, occasional symptoms that do not require medication or medical control; Visick III, frequent symptoms that require medical treatment; and Visick IV, daily symptoms that require vigorous medical treatment or reoperation. Clinical recurrence was defined as a Visick score of III or IV.

- (2) Endoscopic appearance of erosions proximal to the squamocolumnar junction. There was a very close correlation between presence of recurrent symptoms and erosive oesophagitis.

Follow-up

Clinical examination was performed at 15 days, 1 month, 6 months and 1 year after surgery, and then every 12 months. Endoscopy was performed 6–12 months after surgery and at 5 years, or if symptoms recurred. Manometric evaluation was performed 2–6, 60 and 90 months after surgery.

Statistical analysis

For statistical evaluation Fisher's exact test and Mann-Whitney test were employed, $P < 0.05$ was considered significant. For the determination of recurrence the Kaplan-Meier plot was employed.

Results

The clinical and laboratory characteristics of patients in the two groups were similar (*Table 1*). Patients with uncomplicated Barrett's oesophagus were significantly older (mean 50 years) than those with no evidence of Barrett's oesophagus (43 years) ($P < 0.01$).

The early and late outcome is shown in *Table 2*. There were no operative deaths. Postoperative morbidity included two reoperations (one in each group), one owing to postoperative shock and one to trapping of the nasogastric tube by the antireflux stitches. At late follow-up only 5 per cent of the patients could not be evaluated. Four patients died from non-related causes. The mean time to clinical recurrence was similar in both groups (4 years after surgery). The recurrence rate for all patients submitted to fundoplication or calibration of the cardia is shown in *Fig. 1*. At 5 years there was a recurrence rate of approximately 20 per cent for both operations; this increased to 40 per cent for both operations at 10 years (P not significant). There was a significant difference in recurrence rate between patients with and without Barrett's oesophagus, independent of the type of surgical procedure performed (*Fig. 2*). The total recurrence rate at 5 years for patients without Barrett's oesophagus was 15 per cent after fundoplication and 19 per cent after calibration of the cardia ($P > 0.5$), while the

Table 1 Initial clinical and laboratory characteristics

	Fundoplication (n=76)	Calibration of the cardia (n=88)
Sex*		
Men	19 (25)	32 (36)
Women	57 (75)	56 (64)
Age (years)†		
Total	44(7)	45(8)
No Barrett's oesophagus	43(7)	42(7)
Barrett's oesophagus	50(5)	51(6)
Concomitant diseases*		
Gallstones	29 (38)	24 (27)
Cholecystectomy	14 (18)	15 (17)
Duodenal ulcer	7 (9)	3 (3)
Endoscopy*		
Erosive oesophagitis	45 (59)	59 (67)
Barrett's oesophagus	17 (22)	22 (25)
Manometry		
LOS pressure (mmHg)†	8.8(0.6)	7.9(0.6)
Total length (mm)†	32(1.2)	30(1.0)
Abdominal length (mm)†	8.2(0.9)	6.3(0.5)
Incompetent LOS*	49 of 76 (64)	59 of 88 (67)
Reflux studies*		
Abdominal scintiscanning	56 of 61 (92)	51 of 56 (91)
Abnormal 24-h pH study	27 of 27 (100)	34 of 34 (100)

*Values in parentheses are percentages; †values are mean(s.d.). LOS, lower oesophageal sphincter. There were no significant differences between groups

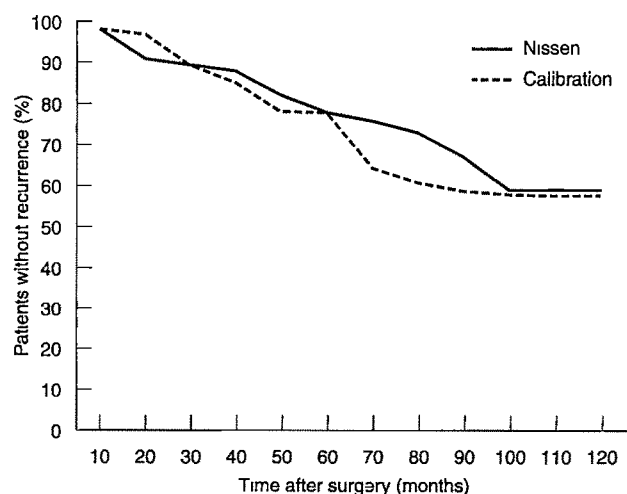
corresponding figures for patients with Barrett's oesophagus were 45 and 57 per cent respectively ($P < 0.000$). The total recurrence rate at 10 years after surgery was 23 per cent after fundoplication and 22 per cent after calibration of the cardia in patients without Barrett's oesophagus ($P > 0.8$), while it was 83 and 80 per cent respectively for patients with Barrett's oesophagus ($P < 0.000$).

A few asymptomatic patients had endoscopic recurrence, four patients after fundoplication (three with severe erosive oesophagitis and one with Barrett's oesophagus plus a peptic ulcer) and five patients after calibration of the cardia (three with severe erosive oesophagitis and two with Barrett's oesophagus and oesophagitis). Five patients developed low-grade dysplasia after surgery: two after Nissen fundoplication a mean of 5.5 years after surgery and three after calibration of the cardia a mean of 5.8 years after surgery. Four of them had symptom recurrence but one was asymptomatic. The endoscopic and manometric results 5 years after surgery in patients with no evidence of Barrett's oesophagus before operation are shown in Table 3. In patients with Visick I and II symptoms late after surgery, both procedures resulted in significant improvement in all endoscopic and manometric parameters ($P < 0.0001$). In contrast, in patients with Visick III and IV grades late after surgery there was no change from the preoperative level in any parameter measured 5 years after surgery.

Table 2 Early and late postoperative outcome

	Fundoplication (n=76)	Calibration of the cardia (n=88)
Operative deaths	0	0
Operative morbidity		
(reoperations)*	1 (1)	1 (1)
Late incisional hernia*	2 (3)	4 (5)
Follow-up		
Lost to follow-up*	4 (5)	4 (5)
Follow-up time (months)†	84(24)	87(22)
Died from unrelated causes*	2 (3)	2 (2)
True late follow-up*	70 (92)	82 (93)
Time to recurrence (months from operation)†	46 (23)	48 (24)
Recurrence at 5 years (%)		
No Barrett's oesophagus	18	22
Barrett's oesophagus	45	57
Recurrence at 10 years (%)		
No Barrett's oesophagus	25	23
Barrett's oesophagus	83	80
Asymptomatic		
Endoscopic recurrence*	4 (5)	5 (6)
Appearance of dysplasia in Barrett's oesophagus		
No. of patients	2 of 17	3 of 22
Mean time after surgery (years)	5.5	5.8

*Values in parentheses are percentages; †values are mean(s.d.). LOS, lower oesophageal sphincter. There were no significant differences between groups

**Fig. 1** Recurrence of gastro-oesophageal reflux in patients who had fundoplication or calibration of the cardia

The endoscopic and manometric late results in patients with GORD and uncomplicated Barrett's oesophagus are shown in Table 4. In the small group of patients with a Visick score of I or II late after surgery, endoscopic and

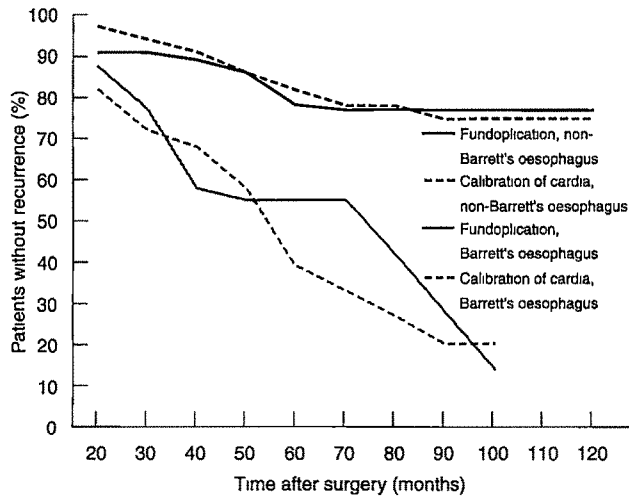


Fig. 2 Recurrence of gastro-oesophageal reflux according to the presence or absence of Barrett's oesophagus

manometric parameters improved significantly after both surgical techniques, apart from the amplitude of the distal contractile waves of the oesophagus, which showed no significant change. Among patients with failure and recurrence, no significant improvement was observed in any laboratory measurement.

Dysphagia was not an important problem in this study: early postoperative dysphagia was reported in 33 per cent of patients after fundoplication and 30 per cent after calibration of the cardia. This symptom persisted in fewer than 5 per cent of the patients.

Manometric evaluation up to 90 months was available in 62 patients included in the present randomized trial (Table 5). In patients without Barrett's oesophagus who were asymptomatic, with a Visick score of I or II late after surgery ($n=38$), LOS pressure increased significantly 2–6 months after surgery and then decreased to a level higher than that observed before surgery, which was maintained

Table 3 Endoscopic manometric late results in patients with gastro-oesophageal reflux disease but no evidence of Barrett's oesophagus submitted to fundoplication or calibration of the cardia with posterior gastropexy

	Fundoplication ($n=53$)				Calibration of the cardia ($n=62$)			
	Visick I–II ($n=39$)		Visick III–IV ($n=14$)		Visick I–II ($n=44$)		Visick III–IV ($n=18$)	
	Preop.	5 years	Preop.	5 years	Preop.	5 years	Preop.	5 years
Endoscopy								
No with oesophagitis	23	0†	14	12	26	0†	18	14
Manometry*								
LOS pressure (mmHg)	9.4(0.8)	15.7(0.9)†	9.8(1.3)	12.3(1.4)	7.3(0.7)	15.8(1.1)†	8.3(0.9)	8.8(1)
Total length (mm)	32(1.4)	41(1.4)†	34(3)	32(2)	32(1.4)	41(1)†	35(2.6)	37(3)
Abdominal length (mm)	7.5(0.6)	16.2(0.7)†	11(3.7)	9.4(0.6)	7.2(0.8)	15.8(1)†	8.2(1)	10.5(1.1)
Amplitude distal oesophageal waves (mmHg)	51(25)	76(36)†	59(36)	71(27)	55(23)	74(32)†	45(24)	50(18)

*Values are mean(s.d.). Visick grades were at late assessment. LOS, lower oesophageal sphincter. † $P<0.0001$ versus preoperative value.

Table 4 Endoscopic and manometric late results in patients with gastro-oesophageal reflux disease and Barrett's oesophagus submitted to fundoplication or calibration of the cardia with posterior gastropexy

	Fundoplication ($n=17$)				Calibration of the cardia ($n=22$)			
	Visick I–II ($n=4$)		Visick III–IV ($n=13$)		Visick I–II ($n=5$)		Visick III–IV ($n=17$)	
	Preop.	5 years	Preop.	5 years	Preop.	5 years	Preop.	5 years
Endoscopy								
No with oesophagitis	2	0	8	8	2	0	11	9
Manometry*								
LOS pressure (mmHg)	8(0.9)	18.3(1.1)†	5.4(1.4)	7.4(2.2)	7.8(2.3)	19(3.4)†	8(1.8)	8.5(1)
Total length (mm)	25(1.2)	37(1.2)†	27(3.7)	26(5.7)	25(5)	35(4)	29(2.4)	36(3)
Abdominal LOS length (mm)	6.5(0.5)	14.3(0.7)†	8.1(3.5)	16(7)	6(2)	16.6(3.2)†	6.3(1.6)	11.2(19)
Amplitude distal oesophageal waves (mmHg)	30(28)	51(29)	45(20)	37(17)	29(29)	38(29)	40(19)	37(24)

*Values are mean(s.d.). Visick grades were at late assessment. LOS, lower oesophageal sphincter. † $P<0.0001$ versus preoperative value.

Table 5 Lower oesophageal sphincter pressure before and late after surgery in 62 patients

Status late after surgery	n	Before operation	Time after surgery (months)		
			2-6	60	90
No Barrett's oesophagus (Visick I-II)	38				
LOS pressure (mmHg)*		8.7(5)	21(7)†	17.6(10)†‡	14(3)†‡
Incompetent LOS		25	3	4	4
No Barrett's oesophagus with recurrence (Visick III-IV)	9				
LOS pressure (mmHg)*		8.6(7)	14(2)	10.8(3)	7.8(3)
Incompetent LOS		7	2	4	6
Barrett's oesophagus	15				
LOS pressure (mmHg)*		9(7)	13.5(8)	12(4)	8.3(5)
Incompetent LOS		10	4	8	11

*Values are mean(s.d.) LOS, lower oesophageal sphincter. † $P < 0.0001$ versus before operation, ‡ $P < 0.05$ versus 2-6 months after operation

Table 6 Twenty-four-hour oesophageal pH monitoring before and after fundoplication or calibration of the cardia (percentage of time during 24 h with intraoesophageal pH < 4)

Visick grade after 5 years	pH monitoring	
	Fundoplication	Calibration of the cardia
I-II		
Before operation	24.8(6) (n=17)	26.3(7) (n=24)
5 years after operation	5.0(2)* (n=13)	3.8(1.6)* (n=20)
III-IV		
Before operation	17.8(10) (n=10)	32.3(12) (n=10)
5 years after operation	27.3(11) (n=6)	19.3(10) (n=7)

* $P < 0.000$ versus preoperative value

for 90 months. The low percentage of patients with incompetent LOS persisted late after operation. On the contrary, in patients with no evidence of Barrett's oesophagus in whom antireflux surgery failed (Visick score III-IV) ($n = 9$), LOS pressure showed a non-significant increase 2-6 months after surgery and by 90 months after surgery it had decreased to a level comparable to preoperative values. The percentage of patients with incompetent LOS increased in parallel to the length of the follow-up. In the 15 patients with uncomplicated Barrett's oesophagus who had surgery, LOS pressure increased 2-6 months after surgery, but then a progressive decrease in sphincter pressure was demonstrated late after surgery, although there were no significant differences. The percentage of patients with incompetent LOS increased with the length of follow-up.

The 24-h oesophageal pH monitoring results before and after surgery are shown in Table 6. Patients with a Visick score of I or II 5 years after surgery showed a significant decrease in the amount of time with oesophageal pH less than 4 after surgery, while patients with recurrence and

Visick scores of III-IV 5 years after operation had no significant changes or even an increase after the operation had failed.

Discussion

The results of the present prospective randomized study suggest that, in order to establish the real clinical benefit of an antireflux procedure, it is important to have a late follow-up. Second, it is necessary to establish subjective and objective evaluations in order to determine the efficacy of antireflux surgery. Third, patients with chronic pathological gastro-oesophageal reflux must be separated into at least two different groups because late results are different for patients with and without Barrett's oesophagus. Late manometric evaluation of LOS pressure can predict late clinical results in patients who had antireflux surgery.

Ten other prospective randomized studies have compared the results of two different antireflux operations. Concerning comparisons of Angelchik and Nissen operations, in all reports^{21-23,25} there were some who had to have the prosthesis removed. Final results were similar in three and better for fundoplication in one study. One study²⁰ compared ten patients who had Nissen fundoplication with ten submitted to the ligament teres cardiopexy. Short-term follow-up demonstrated an 80 per cent failure rate at 1 year with this gastropexy; it should not be used as an antireflux procedure.

Thor and Silander²⁴ compared 19 patients after a Toupet operation with 12 patients after a Nissen procedure who were followed for 5 years. Some 95 per cent of the patients were Visick grade I and II after the Toupet operation compared with 67 per cent after Nissen fundoplication. However, the small number of patients made it very difficult to reach valid conclusions.

Walker *et al.*¹⁹ compared 26 patients after Nissen and 26 patients after Lind partial fundoplication. Mean follow-up was only 13 months, with a maximum of 33 months. Some 35 per cent of patients in the Nissen group had Barrett's oesophagus compared with 42 per cent in the Lind group but no valid conclusions were drawn because of the very short follow-up. Lundell *et al.*²⁶ compared 72 cases after Toupet with 65 after the Nissen technique, with a follow-up of 3 years. Twenty-two patients had Barrett's oesophagus. Both procedures had similar results, with a relapse rate of 5 per cent at 3 years. No late follow-up was considered and no objective parameters were evaluated. Five patients showed intrathoracic herniation. Laws *et al.*¹⁷ reported a randomized trial of the laparoscopic procedure, comparing 23 patients after a Nissen and 16 after a Toupet procedure. Follow-up was short (27 months) and it was not clear whether patients with Barrett's oesophagus were included as there was no objective evaluation of the results. Clinical results were similar in both groups. One of the best randomized studies, comparing three surgical procedures (Nissen, Belsey and Hill procedures, with 15 patients in each group) was first reported in 1974¹⁸. In this study objective evaluations were performed but the number of patients undergoing each technique was small and the follow-up was only 24 months. Better results were seen after Nissen fundoplication for controlling reflux, although all operations increased LOS pressure. Dysphagia was present after the Nissen and Hill procedures but at 6 months it had almost disappeared.

DeMeester *et al.*¹⁸ published late follow-up of 100 patients submitted to Nissen total fundoplication, with a mean follow-up of 43 months. Patients with Barrett's oesophagus were included in the same group. The late clinical assessment demonstrated good to excellent results in 83 per cent, with one operative death and a morbidity rate of 13 per cent. Loustarinen⁵ has the longest follow-up of 108 patients submitted to fundoplication (mean 77 months). In this publication there was no distinction in the results for patients with Barrett's oesophagus. Some 41 per cent of patients had a Visick score of III or IV at late follow-up. Late after surgery 18 patients had Barrett's oesophagus, compared with only six previously. The incidence of oesophagitis increased from 8 per cent at 37 months to 26 per cent at 110 months, stressing the importance of late follow-up. Martinez de Haro *et al.*¹⁰ followed 51 patients with reflux oesophagitis for 6.6 years, including 31 per cent with Barrett's oesophagus. Good results were obtained in 89 per cent of patients but endoscopic recurrence was higher (14 per cent) and pathological acid reflux identified by 24-h pH monitoring after surgery was 20 per cent.

In a previous report from this institution, the late results in 215 patients with GORD submitted to calibration of the cardia and posterior gastropexy were reported¹². No clear distinction was made for Barrett's oesophagus. Final results at 5 years demonstrated that 85 per cent of patients were Visick grades I and II, and 15 per cent of procedures had failed.

In the present trial the following principles were established at the beginning of the study in order to reach valid conclusions: (1) an adequate number of patients, (2) subjective and objective evaluation, (3) late follow-up of 8–10 years, and (4) clear distinction of the results between Barrett's and non-Barrett's patients, although all were submitted to the same surgical procedures.

In this study, which took 13 years, it was demonstrated that patients with long-segment uncomplicated Barrett's oesophagus have a very different outcome from patients without Barrett's oesophagus, independent of the surgical procedure. Both Nissen fundoplication and Hill–Larraín posterior gastropexy with calibration of the cardia had almost identical late overall results. Late high rates of recurrence and appearance of dysplasia occurred in patients with Barrett's oesophagus, while 77 per cent of those without Barrett's oesophagus were Visick grade I and II at 10 years' follow-up. One reason for this difference might be that patients with Barrett's oesophagus have very poor sphincter function, with a high rate of LOS incompetence. Motor function of the distal oesophagus is seriously compromised. This is important and results in delayed clearance of the refluxed material (acid and duodenal juice) from the distal oesophagus. The gastro-oesophageal junction is greatly dilated in this group^{14–16}. Simple antireflux surgery, which only improves and recreates LOS competence, works well in patients without Barrett's oesophagus, with good improvement in LOS function. Late manometric evaluation of the LOS is an important objective parameter that can predict final clinical results. On the contrary, patients with Barrett's oesophagus have inadequate improvement of sphincter function at late follow-up owing to the severe chronic transmural inflammation that compromises the distal oesophagus and the musculature of the LOS^{27,29,30}. During the early period after surgery, LOS function improves and the previously dilated oesophago-gastric junction reduces^{12,36}. However, later on the gastro-oesophageal junction loses its strength and begins to dilate again, with decreased LOS pressure and development of an incompetent LOS aggravated by defective motor function of the distal oesophagus³⁶. Therefore, reflux of acid and duodenal contents occurs again, with recurrence of symptoms and the appearance of dysplasia³⁶.

Patients submitted to antireflux surgery (open or laparoscopic) must be evaluated carefully before operation to

determine whether or not they have a Barrett's oesophagus. If Barrett's oesophagus is not detected, they are ideal candidates for a simple antireflux procedure. On the contrary, if Barrett's oesophagus is present, other medical or surgical alternatives might be considered.

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Treatment of recurrent colorectal liver metastases by interstitial laser photocoagulation

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Background: Hepatic resection improves survival in selected patients with colorectal liver metastases. The treatment of recurrent hepatic metastases after resection is controversial. Interstitial laser photocoagulation, performed under local anaesthesia, offers a minimally invasive option to repeat resection. The first series of patients with recurrent colorectal liver metastases treated with photocoagulation is reported.

Methods: Nineteen patients (five women and 14 men, median age 57 (range 44-71) years) who developed recurrent colorectal liver metastases after hepatectomy (five with bilateral disease) were treated with photocoagulation between 1993 and 1997. Fifteen patients also received chemotherapy (14 systemic, one hepatic arterial) before photocoagulation.

Results: There were no major complications or deaths related to the treatment. Six patients developed minor complications related to the procedure but did not require any form of intervention. Median survival from commencement of photocoagulation was 16 (range 4-36) months.

Conclusion: Photocoagulation is a safe, minimally invasive therapy that may be used as an adjunct to chemotherapy and repeat resection in the treatment of recurrent colorectal liver metastases, and may lead to improved survival.

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Introduction

Liver resection remains the most effective form of treatment for patients with colorectal liver metastases^{1,2}. The 3-year median survival in this unit is 60 per cent with a 5-year survival rate of approximately 25 per cent. Following resection a proportion of patients will develop hepatic recurrence either at the resection site or in the contralateral lobe. Treatment of such recurrence remains controversial, with some advocating repeat resection^{3,4}. In those in whom repeat resection is not feasible, chemotherapy produces poor results.

In situ ablation techniques, such as cryotherapy, alcohol injection and interstitial laser photocoagulation, have been described in the treatment of patients with hepatic tumours⁵⁻⁷. Cryotherapy requires a laparotomy; although a laparoscopic technique is now available, it has been associated with a number of complications⁶. Alcohol injection is of use in treating hepatocellular carcinoma (HCC) but is of less value in the treatment of colorectal liver metastases.

Photocoagulation involves delivery of high-energy light to the tumour resulting in thermal injury. Up to eight laser fibres are positioned in the tumour centre, using image guidance, resulting in controlled areas of tissue destruction^{5,8}. The procedure is performed under local anaesthetic and intravenous sedation. Photocoagulation has been shown to be both safe and effective for treating irresectable colorectal liver metastases⁵, although its use has never been assessed in the treatment of recurrent tumours.

The aim of this study was to assess the use of photocoagulation in patients who had developed recurrent colorectal liver metastases after previous hepatic resection and who were considered unsuitable for further resection.

Patients and methods

Nineteen patients (five women and 14 men, median age 57 (range 44-71) years), who presented with recurrent colorectal liver metastases following liver resection, were treated with photocoagulation between 1993 and 1997. None was

considered suitable for repeat resection. Resectability was defined as unilateral disease confined to the liver.

Fifteen patients had received chemotherapy consisting of 5-fluorouracil and folinic acid (14 systemic and one hepatic arterial) between the diagnosis of recurrence and commencement of photocoagulation.

The histology of the primary tumour was Dukes B in two patients and Dukes C in nine; the remainder had synchronous liver metastases (Dukes 'D'). All patients had undergone previous hepatic resection (ten right hepatectomies, seven segmentectomies, one left hepatectomy and one wedge resection) and had developed hepatic recurrence (five bilateral and 14 unilateral) with a median time from hepatic resection to diagnosis of recurrence of 9 (range 4–34) months. All patients underwent spiral computed tomography (CT) to stage the disease and were reviewed in a multidisciplinary meeting consisting of surgeons, radiologists and oncologists with an interest in colorectal malignancy.

Photocoagulation was performed under local anaesthetic (0.5 per cent bupivacaine) and conscious sedation using a Diomed (Diomed, Cambridge, UK) 25 laser (805 nm, 2–2.7 W per fibre). Up to eight hollow 19-G needles (Cook, Hertfordshire, UK) were positioned using ultrasonography in combination with either CT or magnetic resonance imaging (MRI). Once the needles had been placed satisfactorily within the tumour, the laser fibres were inserted down the needles such that the tip of the laser fibre protruded 5 mm beyond the end of the needle. Up to 75 000 J was delivered per treatment session. CT or MRI was performed after treatment to monitor response and repeated 2 months later. Eleven patients underwent two treatment sessions, five had three, two had four and one had five sessions.

Results

Six patients developed complications related to the procedure. There were no deaths related to the treatment. Two patients developed pleural effusions, one a biloma, one a subcapsular haematoma, one a small asymptomatic pneumothorax and one a tumour nodule at a needle puncture site which was later excised. *Fig. 1* illustrates a recurrent colorectal liver metastasis in the left lobe after previous right hepatectomy before and after photocoagulation treatment, and demonstrates laser-induced necrosis at the tumour site. The median survival from commencement of photocoagulation treatment was 16 (range 4–36) months.

Discussion

Recurrence of colorectal liver metastases after resection poses a considerable problem in management. If possible,

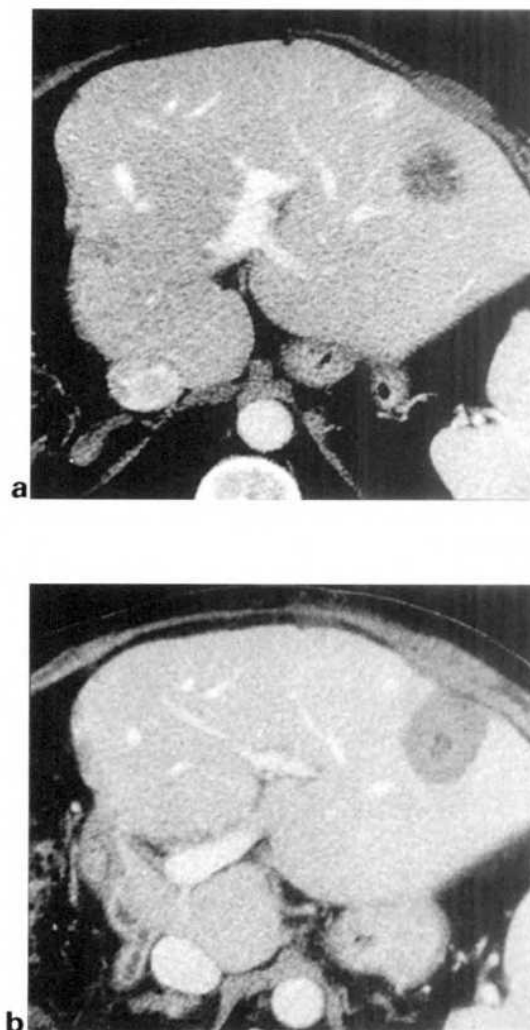


Fig. 1 Computed tomography of the liver of a patient with recurrent colorectal metastases after previous right hepatectomy.
a Recurrent disease in the contralateral lobe.
b Necrosis in the tumour after a single session of interstitial laser photocoagulation treatment

further resection appears to offer the greatest long-term survival, although in many instances this will not be feasible^{3,4}. For patients in whom further resection is impossible, chemotherapy provides little in terms of palliation.

Physical methods of tumour ablation such as cryotherapy, alcohol injection and photocoagulation have been described for treating hepatic tumours. Cryotherapy necessitates a laparotomy in order to apply the cryoprobe (although laparoscopic devices are now available) and can only be applied to superficial lesions or used as an adjunct to

hepatic resection. It has also been associated with a range of complications, some of which are life threatening^{6,7}. Alcohol injection is useful in the management of HCC but is of little value in the treatment of colorectal liver metastases.

Photocoagulation was first described by Bown in 1983⁸ and Hashimoto *et al.*⁹ reported the first clinical study in 1985. They treated two patients with HCC and eight patients with liver metastases during laparotomy under ultrasonographic guidance. More recent percutaneous approaches, again under ultrasonographic guidance, have been described by Huang *et al.*¹⁰. They treated five patients with small HCC and later confirmed laser-induced necrosis with ultrasonographically guided biopsies. Masters *et al.*¹¹ reported treatment of 18 liver metastases in ten patients with photocoagulation, and demonstrated a response rate of over 44 per cent with CT and guided biopsies. Amin *et al.*⁵ also demonstrated a favourable response rate in 26 patients with 70 hepatic metastases.

In this study, photocoagulation has been demonstrated to be a safe adjunct to chemotherapy in patients with recurrent colorectal liver metastases. None of the minor complications required intervention except excision of a skin nodule. Treatment under local anaesthetic allowed patients to return to normal activity within a few days, which is important considering the palliative nature of the treatment.

The survival advantage gained with this treatment is hard to assess given the small numbers and heterogeneous nature of the patients studied. Many patients have received a variety of treatments for varying degrees of hepatic replacement. The 3-year survival rate from resection of the original metastases compares favourably with that of patients undergoing hepatic resection who do not develop hepatic recurrence^{1,2}. These results are similar to those obtained for many patients undergoing repeat resection of recurrent colorectal liver metastases but without the morbidity of open surgery^{3,4}.

Photocoagulation offers a minimally invasive and safe technique which should be considered in the treatment of patients with recurrent colorectal liver metastases. Survival appears to be improved using this treatment and compares favourably with that associated with other treatments currently used in this patient group.

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Relationship of carotenoid and vitamins A and E with the acute inflammatory response in acute pancreatitis

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Background: Inflammation and oxidative stress are believed to be important in the development of the systemic complications of acute pancreatitis. The fat-soluble vitamins A and E, and the carotenoids have antioxidant properties. The aim of this study was to assess the effect of acute pancreatitis on serum concentrations of vitamin antioxidants and to relate such changes to the degree of the inflammatory response.

Methods: Thirteen consecutive patients with predicted severe acute pancreatitis were compared with 26 matched healthy controls. Five patients developed severe acute pancreatitis and three of these died. Vitamin antioxidant and C-reactive protein (CRP) levels were measured daily for up to 7 days.

Results: Patients had significantly lower levels of antioxidants throughout the course of the study ($P < 0.017$). In patients there was a significant correlation between peak CRP and trough antioxidant levels ($P < 0.01$). In patients with mild acute pancreatitis, the concentrations of retinol and β -carotene at final review were significantly higher than those in patients with severe acute pancreatitis ($P < 0.05$). This coincided with a reduction in CRP level.

Conclusion: In acute pancreatitis, circulating concentrations of vitamin antioxidants are reduced and are inversely related to the rise in CRP level.

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Introduction

The systemic complications of acute pancreatitis are similar to those seen in the systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndrome. These usually occur within the first 7–10 days and are the major cause of death associated with the disease^{1,2}. The inflammatory response occasioned by acute pancreatitis results in the activation of peripheral blood mononuclear cells and the release of chemical mediators such as tumour necrosis factor, interleukin 8 and platelet activating factor. Polymorphonuclear leucocytes are activated and secrete reactive oxygen intermediates or oxygen free radicals (respiratory burst) which interact with intracellular enzyme and signalling pathways resulting in tissue damage^{3–7}. Free radical-induced cellular damage may result in increased cell membrane permeability, enzyme inhibition, calcium influx and increased capillary permeability, features of the SIRS. This oxidative stress is increasingly recognized as playing a major role in the pathogenesis of many inflammatory disorders, including acute pancreatitis^{8–12}.

C-reactive protein (CRP) is an acute-phase protein produced by the liver. It has been shown to reflect the

degree of inflammatory insult, and peak CRP concentration may be used as a predictor of disease severity^{13,14}. The lipid-soluble vitamins A and E, and the carotenoids are important, plant-derived antioxidants. There is increasing interest in their capability of quenching oxygen-derived free radicals. Although several studies have looked at the antioxidants vitamin C and glutathione in human and experimental acute pancreatitis^{11,15}, the effect of the disease on vitamins A and E has primarily been studied in animal models¹⁶. The aim of this study was to examine the effect of acute pancreatitis on serum vitamin A and E and carotenoid concentrations, and to relate these changes to the inflammatory response as measured by CRP levels.

Patients and methods

Thirteen patients with predicted severe acute pancreatitis were compared with 26 control patients. Patients were included if they were within 72 h of the onset of symptoms, had a biochemical and clinical picture consistent with the diagnosis and had predicted severe disease as defined by an Acute Physiology And Chronic Health Evaluation

(APACHE) II score greater than 5, three or more positive Glasgow prognostic indicators¹⁷ or a CRP level above 120 mg/l. There were six men and seven women with a median age of 64 (range 35–80) years. Five patients had alcohol-induced acute pancreatitis, five gallstone-related pancreatitis and three were considered to have idiopathic acute pancreatitis. The median APACHE II score at study entry was 10 (range 7–20) (Table 1). Five patients developed severe acute pancreatitis as defined by the Atlanta criteria¹⁸ during the 7 days of the study; four patients had respiratory impairment and one had both respiratory and renal failure. Three patients died, as a consequence of pancreatitis.

The 26 control patients were healthy outpatients attending a routine health screening clinic. There were 13 men and 13 women with a median age of 59 (range 40–73) years. All control patients were fasting, free of disease and were not taking medication likely to affect antioxidant metabolism.

Experimental design

Patients were reviewed daily from study admission for 7 days, unless hospital discharge or death occurred earlier. At each review a 5-ml sample of venous blood was taken and mixed with lithium heparin (Vacutainer; Becton Dickinson, Plymouth, UK) for the measurement of antioxidant levels, and a 10-ml sample was taken for routine biochemical analysis and CRP measurement. All plasma samples were stored at –70°C until analysed.

Analytical methods

Plasma vitamin A, carotenoid and vitamin E concentrations were measured by high-performance liquid chromatography, using the method developed by Olmedilla *et al.*¹⁹. Serum was separated by centrifugation and deproteinized with ethanol containing internal standards. Vitamins A, E and the carotenoids were extracted with hexane and the hexane then evaporated. The residue was dissolved in developing solvent and a 20- μ l aliquot injected on to a C18 (5- μ m microbore 0.32 $\times$ 25 cm) reverse-phase chromato-

graphic column (Phenomenex, Macclesfield, UK). The mobile phase (75 : 20 : 5 methanol : acetonitrile : tetrahydrofuran containing 0.1 per cent ascorbic acid) was pumped at 0.6 ml/min. Vitamin A and E peaks were detected at 325 and 295 nm respectively, and the carotenoids at 450 nm, using a Waters multiwavelength detector (Waters, Milford, Massachusetts, USA). The precision (coefficient of variation) of this technique was less than 9 per cent intrabatch and less than 16 per cent interbatch for all analytes.

The compounds assayed were: retinol (vitamin A), α -carotene, β -carotene, lutein, lycopene and α -tocopherol (vitamin E). CRP was measured by fluorescence polarization immunoassay, using an Abbott TDX analyser and Abbott reagents (Abbott Laboratories, Abbott Park, Illinois, USA). The lower limit for detection of this assay is less than 5 mg/l.

Statistical analysis

Statistical analysis was carried out using SPSS 6.0 for Windows (SPSS, Chicago, Illinois, USA). Non-parametric analysis of data was performed using the Mann–Whitney U test and the Wilcoxon matched pairs signed rank test for paired data. The relationship between CRP and antioxidant levels was examined using the Spearman rank correlation test. For paired data, $P < 0.05$ was taken as significant. For multiple comparisons against a single control, the Bonferroni correction was made and $P < 0.017$ was considered to be significant.

Results

There was no significant difference in either age or sex distribution between the patient and control groups.

Antioxidant levels

The antioxidant level on admission to the study, the trough level over the subsequent days and the concentration on the final day of review were examined (Tables 2 and 3). Median length of review was 4 (range 1–7) days.

The admission, trough and final levels of all antioxidants measured were significantly reduced in patients compared with controls (Table 2).

There was no significant difference between either the admission or trough levels of antioxidants in patients who developed complications and those who did not. Patients with mild acute pancreatitis had significantly higher levels of retinol and β -carotene at final review than those with severe pancreatitis (Table 3).

There was no significant difference in carotenoid levels between the various aetiological groups.

Table 1 Organ dysfunction and Acute Physiology And Chronic Health Evaluation score at study entry

	No. of patients	APACHE II score
No organ dysfunction	8	7, 8, 8, 8, 8, 10, 11, 14
One organ failing/failed	2	12, 15
Two organs failing/failed or died	3	17, 19, 20

APACHE, Acute Physiology And Chronic Health Evaluation

Table 2 Antioxidant and C-reactive protein concentrations in healthy controls and patients with acute pancreatitis

	Controls (n=26)	All patients with pancreatitis (n=13)		
		Admission	Trough (peak CRP)	Final day
Retinol ($\mu\text{mol/l}$)	2.0 (1.1–3.0)	1.1 (0.2–2.4)*	0.6 (0.1–1.4)*	1.0 (0.1–2.0)*
α -Tocopherol ($\mu\text{mol/l}$)	37.0 (5.7–54.0)	20.0 (8.0–45.0)*	13.0 (8.0–45.0)*	18.0 (8.0–49.0)*
α -Carotene ($\mu\text{mol/l}$)	4.8 (1.5–16.0)	1.0 (1.0–6.3)*	1.0 (<1.0–2.2)*	1.0 (<1.0–5.7)*
β -Carotene ($\mu\text{mol/l}$)	14.0 (7.0–57.0)	8.0 (2.0–26.0)*	4.0 (1.0–14.0)*	7.0 (<1.0–19.0)*
Lutein ($\mu\text{mol/l}$)	11.5 (5.0–20.0)	6.0 (1.0–16.0)*	4.0 (<1.0–9.0)*	5.0 (<1.0–17.0)*
Lycopene ($\mu\text{mol/l}$)	14.5 (5.0–41.0)	4.0 (1.0–26.0)*	4.0 (<1.0–13.0)*	4.0 (<1.0–26.0)*
CRP ($\mu\text{mol/l}$)	0 (0–4)	83 (14–289)*	218 (63–293)*	129 (14–281)*

Values are median (range). CRP, C-reactive protein. * $P < 0.017$ versus controls (Mann–Whitney U test)

Table 3 β -Carotene, retinol and C-reactive protein concentrations in patients with mild and severe acute pancreatitis

	Controls (n=26)	Mild (n=8)			Severe (n=5)		
		Admission	Trough (peak CRP)	Final day	Admission	Trough (peak CRP)	Final day
Retinol ($\mu\text{mol/l}$)	2.0 (1.1–3.0)	1.0 (0.2–1.6)	0.8 (0.2–1.4)	1.4 (0.4–2.0)*	1.1 (0.2–2.4)	0.5 (0.1–0.8)	0.8 (0.1–1.0)*
β -Carotene ($\mu\text{mol/l}$)	14.0 (7.0–57.0)	8.5 (2.0–26.0)	6.0 (2.0–14.0)	9.5 (2.0–19.0)*	8.0 (2.0–14.0)	2.0 (1.0–7.0)	2.0 (<1.0–2.2)*
CRP ($\mu\text{mol/l}$)	0 (0–4)	83 (32–177)	129 (63–226)*	34 (14–218)*	123 (14–289)	264 (218–293)*	213 (98–281)*

Values are median (range). CRP, C-reactive protein. * $P < 0.05$ versus severe at the same time point (Mann–Whitney U test)

C-reactive protein

Patients had significantly higher CRP levels at study entry ($P \leq 0.001$) and throughout the study ($P \leq 0.001$) than controls. On day 1 there was no significant difference in CRP levels between the mild and severe pancreatitis groups. As expected there was a significant difference in the peak CRP value and the final day level between the two patient groups. All the antioxidant levels had a significant negative correlation with CRP ($P \leq 0.005$); the strongest correlation was observed with α -carotene (Table 4).

Table 4 Spearman rank correlation coefficients of minimum antioxidant levels with peak C-reactive protein level

	r_s	P^*
Retinol	–0.46	0.005
α -Tocopherol	–0.52	0.001
α -Carotene	–0.80	<0.001
β -Carotene	–0.69	<0.001
Lutein	–0.57	<0.001
Lycopene	–0.66	<0.001

*Spearman rank correlation test

Discussion

The aim of this study was to assess the effect of acute pancreatitis on the antioxidant vitamins A and E, and the carotenoids in a series of human patients. The patient and control groups were well matched for both age and sex distribution, so any effect of increasing age or differences in male to female ratio should not have caused the significant differences observed. Also the vitamin and carotenoid results for the controls agreed with the normal ranges quoted for the extraction technique used.

In human studies, oxidative stress and the inflammatory response have been assessed either directly by an increase in markers of lipid peroxidation or indirectly by measuring a reduction in the levels of naturally occurring antioxidants

during the course of the illness. Scott *et al.*¹⁵ noted that patients with acute pancreatitis had significantly lower ascorbic acid and vitamin C levels than matched controls, together with a reduced ascorbic acid to vitamin C ratio. It was questioned whether such low levels reflected an inadequate premorbid intake but, using dietary evidence from previous studies, it was concluded that they were likely to result from sequestration into blood cells or the pancreas, or reflect increased urinary excretion. The results suggested that oxidative stress was present by the time patients were admitted, but did not depend on either the aetiology or the severity of the inflammatory process.

The present study looked at the fat-soluble vitamins A and E, and the carotenoids. Vitamin E plays a vital role in

the protection of cellular membranes from free radical-induced damage and when incorporated into lysosomal membranes suppresses the oxidation of phospholipids mediated by free radicals^{20,21}. Vitamin E also influences the response of cells to oxidative stress²². Antosiewicz *et al.*¹⁶ found a decrease in serum level of vitamin E in an animal model of oedematous pancreatitis. An increase in the level of vitamin E in pancreatic tissue was also noted, suggesting redistribution rather than consumption as the cause of the lower serum level. The present study found similarly reduced serum levels of vitamin E in patients compared with controls. Pancreatic biopsies or post-mortem examinations were not routinely performed, so it is not possible to comment on whether this reflected raised pancreatic levels. However, the minimum vitamin E concentrations correlated significantly and inversely ($P \leq 0.001$) with the maximal CRP levels, suggesting that the degree of inflammation is important in determining such concentrations.

Vitamin A and the carotenoids are also known to have antioxidant activity and the results for these show a similar pattern to those for vitamin E. In particular, significant negative correlations were evident between trough vitamin concentrations and maximal CRP levels. In the severe pancreatitis group, however, admission values for the carotenoids lutein and α -carotene were not significantly lower than those for controls. This may reflect the relatively small sample size, with the data skewed by one patient who had much higher values on admission than the other patients. Alternatively, as lutein is the least reactive of the carotenoids it may respond to oxidative stress at a significantly slower rate or to a lesser degree than the other carotenoids. A study of antioxidant levels and the acute-phase protein response in patients with non-small cell lung cancer also found lutein to respond less than the other carotenoids²³.

Patients in the present study were reviewed while they were inpatients, up to a maximum of 7 days. Most patients with mild pancreatitis recover within 72 h and in this study all were discharged within the 7 days of review. In these patients the majority of trough antioxidant levels occurred on day 2 compared with day 4 in the severe group. This may indicate that the initial insult is less sustained in mild compared with severe cases. A significant reduction or improvement in CRP level from the maximum value to the value on the last day of review also matched the clinical recovery of patients with mild pancreatitis; interestingly, there was a significant recovery in the levels of β -carotene and retinol in patients with mild pancreatitis by the final day but not in those with severe disease ($P < 0.05$) (data not shown). This observation is consistent with an inflammatory influence on antioxidant vitamin concentrations, as CRP levels in the severe group showed no improvement from day 1 to final review.

The only source of vitamin A, vitamin E and the carotenoids is dietary. Patients were not required to complete dietary questionnaires on admission, as retrospective dietary assessments are often incomplete and unreliable. The antioxidant levels were similar in groups of patients with idiopathic, gallstone-related or alcohol-induced pancreatitis. This suggests that neither the premorbid diet nor alcohol intake has a significant effect on the levels seen.

It is concluded that significantly lower levels of the carotenoids, vitamin A and vitamin E are found in patients with acute pancreatitis than in healthy controls, and that trough antioxidant levels correlate significantly and inversely with peak CRP concentrations. These observations suggest that the circulating concentrations of these antioxidants are reduced as part of the inflammatory response. Further study is required to address the question of vitamin antioxidant metabolism during acute inflammatory stress associated with acute pancreatitis.

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Radical resection of hilar bile duct carcinoma and predictors of survival

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Background: Patients with carcinoma of the main hepatic duct have a poor prognosis. This study attempted to identify clinicopathological predictors of survival after resection.

Methods: A retrospective review was performed of 114 patients who presented with hepatic ductal carcinoma between 1976 and 1998. Of the 114 patients, 98 had a radical resection, three underwent palliative resection and 13 were not treated surgically. Forty-six patients with stage IVA disease had microscopic tumour residue after resection. Of these, 28 patients were treated with radiotherapy and the remaining 18 had resection alone.

Results: The overall operative morbidity and mortality rates were 14 and 4 per cent respectively. The overall 5-year survival rate after resection was 28 per cent. Nineteen patients survived for more than 5 years, including ten with stage IVA disease. The main prognostic factors were performance status; jaundice; tumour location; gross appearance; histological grade; T, N and M categories in tumour node metastasis (TNM) classification; TNM stage; and residual tumour. Adjuvant radiotherapy, tumour extension into the hepatic ducts, histological grade, N and residual tumour were independent predictive factors by multivariate Cox analysis.

Conclusion: This study suggests that radical resection provides the best survival rate for patients with hilar bile duct carcinoma. For patients with stage IVA disease, following complete gross resection radiotherapy improved treatment outcome.

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Introduction

Although the majority of patients with main hepatic duct carcinoma present at a late stage of the disease resulting in a poor prognosis, recent reports suggest that radical resection may improve the long-term survival of these patients¹. However, the treatment strategy for patients with this disease remains unclear. Since the number of patients is small, predictors of survival after surgical resection have not been sufficiently defined.

This retrospective study was undertaken to identify the clinicopathological factors that significantly influence the long-term survival and operative morbidity and mortality rates of patients with main hepatic duct carcinoma. The efficacy of adjuvant radiotherapy was also examined. This study may provide vital information for deciding when radical surgical management for advanced cancer is justified and when it should be combined with radiotherapy.

Patients and methods

Between October 1976 and December 1998, 114 consecutive patients with main hepatic duct carcinoma, defined as cancer originating from and/or infiltrating the main hepatic ducts², but not reaching the intrapancreatic bile duct, were treated. Of the 114 patients, 101 (89 per cent) underwent surgical resection and 13 did not because of advanced disease or poor medical condition. Patients were followed up for a mean of 939 (range 1–8452) days. Preoperative performance status was determined during the period between biliary drainage and surgery by the criteria established by the Japan Society for Cancer Therapy³. Male patients ($n = 64$) outnumbered female patients ($n = 37$); the mean age was 63.5 (range 19–83) years. The tumours were classified by the tumour node metastasis (TNM) classification criteria⁴. Of the 114 patients, 101 had jaundice on admission; the preoperative maximum total serum bilirubin level ranged

Table 1 Resection procedures according to tumour node metastasis stage grouping

Resection procedures (<i>n</i> = 101)	Total no.	Stage I (<i>n</i> = 4)	Stage II (<i>n</i> = 18)	Stage III (<i>n</i> = 7)	Stage IV (<i>n</i> = 72)	
					IVA (<i>n</i> = 62)	IVB (<i>n</i> = 10)
BDR	35	2	8	6	17	2
BDR + bisegmentectomy	24	1	3	1	17	2
BDR + hepatic lobectomy	31	0	2	0	24	5
BDR + PD	7	0	5	0	2	0
BDR + bisegmentectomy + PD	3	1	0	0	1	1
BDR + hepatic lobectomy + PD	1	0	0	0	1	0

BDR, bile duct resection from the right and left main hepatic ducts to the intrapancreatic bile duct, segmentectomy, resection of the inferior portion of segment 4 and 5 with or without segment 1, occasionally with resection of segment 8 PD, pancreaticoduodenectomy

Table 2 Major postoperative complications

Major complications	Total no. of patients	Bile duct resection with hepatectomy (<i>n</i> = 59)	Bile duct resection without hepatectomy (<i>n</i> = 42)
Liver failure	5	5	0
Anastomotic leakage	1	1	0
Sepsis	5	4	1
Liver abscess	5	3	2
Multiple organ failure	4	4 (2)	0
Gastrointestinal bleeding	1	0	1 (1)
Intra-abdominal bleeding	2	2	0
Pyothorax	1	1	0
Pulmonary infarction	1	1 (1)	0
Liver infarction	3	3	0
Total no. with complications	14	11	3

Values in parentheses are deaths within 30 days

from 12 to 780 (mean 287) $\mu\text{mol/l}$. After percutaneous transhepatic drainage, resection was performed following routine diagnostic imaging.

Resection procedures and indications

Bile duct resection was conducted in 101 patients. In addition to bile duct resection, a variety of other resections were performed (*Table 1*). Pancreaticoduodenectomy was conducted for patients with extensive peripancreatic lymph node metastases, even if the tumour did not extend directly into the intrapancreatic bile duct. The inferior portions of segments 4 and 5 were resected (bisegmentectomy) when the tumour extended into these segmental branches, when the involved hepatic parenchyma was within the resection margin, or when the tumour extended bilaterally to the main hepatic bile ducts without concomitant direct liver invasion beyond the scope of bisegmentectomy. Hepatic lobectomy was performed when the tumour invasion

Table 3 Tumour node metastasis stage grouping of 101 patients who underwent resection

	N ₀ M ₀ (<i>n</i> = 54)	N ₁ M ₀ (<i>n</i> = 15)	N ₂ M ₀ (<i>n</i> = 22)	N ₀ M ₁ (<i>n</i> = 1)	N ₂ M ₁ (<i>n</i> = 9)
T ₁ (<i>n</i> = 4)	4*	0‡	0‡	0	0
T ₂ (<i>n</i> = 28)	18†	4‡	3‡	0	3
T ₃ (<i>n</i> = 69)	32§	11§	19§	1	6

Lymph node metastasis beyond N₂ is classified as M₁. *Stage I; †stage II;

apparently extended beyond the scope of bisegmentectomy. This procedure was also performed when the portal vein could not be reconstructed because of tumour involvement. The caudate lobe was resected when the tumour extended to the corresponding branches. All lymph nodes in the hepatoduodenal ligament, periduodenal area, around the common hepatic artery and on the right side of the coeliac artery were resected. Nodes of the periportal portion

beneath the pancreas, the right side of the superior mesenteric artery and of the intra-abdominal aorta from just below the liver to below the bifurcation of the left renal vein were dissected routinely for patients with swollen N₂ nodes. The portal vein and/or hepatic artery of 32 patients were reconstructed following resection.

Radiotherapy adjuvant to surgical resection

Adjuvant radiotherapy was performed as reported previously⁵. A single dose of intraoperative radiation ranging from 15 to 35 (mean 20.7) Gy was delivered to the tumour bed just after the resection. Postoperative radiotherapy was administered when pathological evaluation demonstrated positive surgical margins. Some 6–8 weeks after resection, a mean total dose of 42.4 Gy was administered using a fraction size of 1.8–3.0 Gy.

Statistical analysis

Survival curves were estimated by the Kaplan–Meier method and the differences between groups were determined by the log rank test. Univariate and multivariate analyses under the Cox proportional hazard model were performed to determine the prognostic factors. With regard to the multivariate Cox regression, the TNM stage grouping and its defining categories were not used simultaneously because of the high correlation coefficients between TNM and those categories⁶. Adjuvant radiotherapy was excluded from this multivariate analysis because 48 (86 per cent) of 56 patients who received radiotherapy had stage IV disease. $P < 0.05$ was considered statistically significant.

Results

Operative morbidity and mortality rates

Major complications occurred in 14 of the 101 patients who underwent resection. Liver abscess, sepsis and hepatic failure were the most frequent complications followed by multiple organ failure. The major complication and 30-day operative death rates were significantly higher in patients who underwent hepatectomy (19 and 5 per cent respectively) than in those who did not (three (7 per cent) and one (2 per cent) of 42 patients respectively) (*Table 2*). Between days 41 and 140 after operation, five patients died from surgical complications with or without progressing persistent and/or newly developed distant metastasis. The overall 30-day operative mortality rate was 4 per cent (four of 101 patients).

Histopathological findings, correlation of cholangiographic tumour location and pathological T category

Of the 114 patients, one patient had squamous cell carcinoma and did not undergo resection. The remaining 113 had adenocarcinoma. Of the 101 resected patients four had stage I, 18 stage II, seven stage III, 62 stage IVA and ten stage IVB disease. None of the T₁ tumours had metastasis; ten of 28 T₂ and 36 of 69 T₃ tumours had metastasized to the regional lymph nodes. Distant metastases in the nodes and/or on the liver and the peritoneum were found in three of 28 T₂ and 10 per cent of T₃ tumours (*Table 3*).

Based on the cholangiographic findings the tumour extension into the hepatic ducts was classified by Bismuth type⁷. This type correlated significantly with the T category, which represents the depth of cancer invasion into the surrounding tissues and structures of the bile duct (simple kappa coefficient 0.623; $P < 0.05$). Of the 98 patients who underwent radical resection, 23 of the 30 patients with Bismuth I or II type lesions were found to have T₁ or T₂ category tumour by pathological examination. In contrast, 59 (87 per cent) of the 68 patients with Bismuth III or IV lesions had T₃ and the remaining nine patients (13 per cent) had T₁ or T₂ tumours.

Curability of resections

Radical resections were conducted in 98 patients, but potentially curative resection was achieved in only 14. Such resections were defined as having no residual tumour at the microscopic level, no cancer cell invasion in the surgical margins and all lymph node metastases restricted to the scope of the dissection (R₀). Although gross tumours were completely resected in 69 patients, there was microscopic involvement in the surgical margin (R₁). In the remaining 18 patients, tumour invasion was visible in the surgical margins (R₂). In patients with positive surgical margins, the cancer cells were most frequently found on the dissected margin of the tumour in the transverse plane. Invasion was also commonly found in the cut edge of the hepatic duct in the hepatic direction and the cut edge of the bile duct. The incidence of cancer cell invasion into the above three margins in 87 patients who underwent R₁/R₂ resection was 94 per cent ($n = 82$), 77 per cent ($n = 67$) and 30 per cent ($n = 26$) respectively.

Survival and prognostic factors

None of the 13 patients who did not undergo tumour resection survived for more than 3 years; their 2-year survival rate and median survival time were 8 per cent and

Table 4 Factors significantly related to survival (univariate analysis)

Prognostic factor	No. of patients	5-year survival rate (%)	Median survival (days)	P§
Performance status ³				0.0106
PS1, PS2	14	47	1335	
PS3	68	28	716	
PS4	19	10	207	
Preoperative maximum bilirubin ($\mu\text{mol/l}$)				0.0432
<162.5	30	33	1132	
≥ 162.5	71	26	501	
Tumour localization (Bismuth type) ⁷				0.0352
I	9	73	2229	
II	21	36	1132	
III	40	23	413	
IV	31	16	491	
Gross appearance				0.0263
Polypoid	8	73	2229	
Non-polypoid	93	24	622	
Histological grade ⁴				0.0018
G ₁	63	38	971	
G ₂	24	0 (15)*	710	
G ₃ , G ₄	14	0 (17)†	207	
Primary tumour ⁴				0.0062
T ₁	4	75	2043	
T ₂	28	39	1273	
T ₃	69	20	482	
Regional lymph nodes ⁴				<0.0001
N ₀	55	39	1273	
N ₁	15	29	811	
N ₂	31	6	347	
Distant metastasis ⁴				0.0144
M ₀	91	30	746	
M ₁	10	0 (12)‡	130	

*Four-year survival rate, †3-year survival rate, ‡2-year survival rate. PS, performance status. §Log rank test

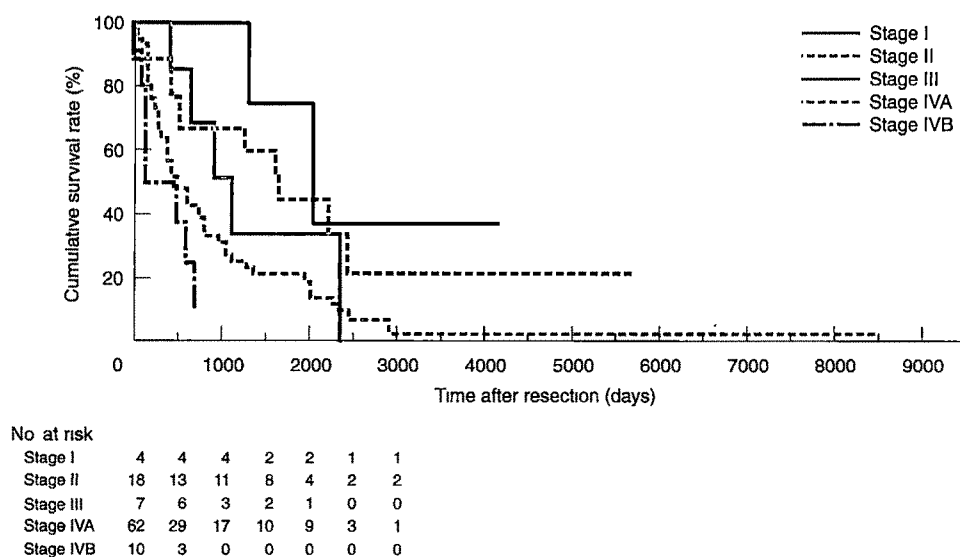


Fig. 1 Survival curves after resection in main hepatic duct carcinoma in accordance with tumour node metastasis stage grouping. $P=0.0038$ (log rank test)

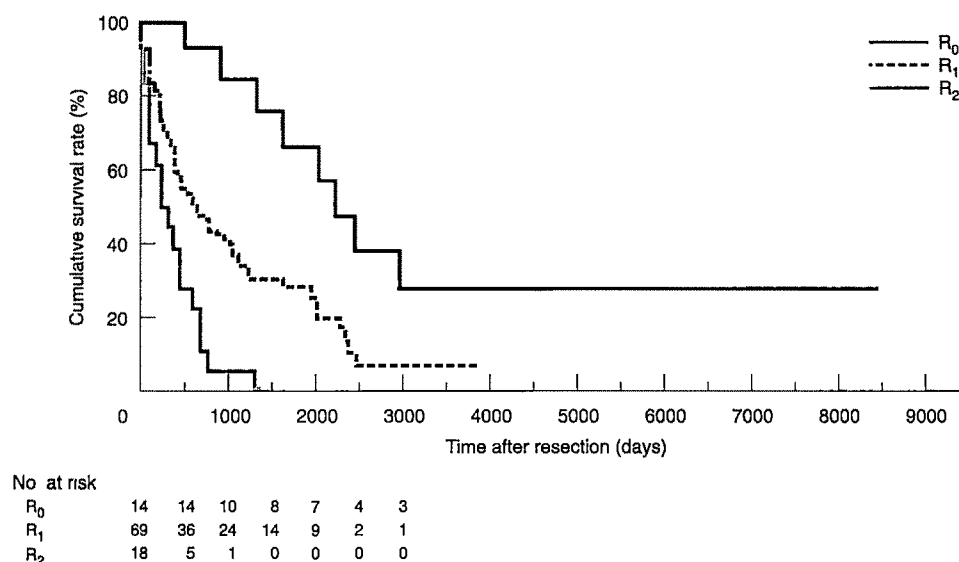


Fig. 2 Survival curves in patients with no tumour residue (R₀ resection), microscopic residue (R₁) and macroscopic residue (R₂) after tumour resection. $P < 0.0001$ (log rank test)

Table 5 Significant risk factors affecting survival after resection (Cox multivariate analysis)

Variable	β coefficient	Standard error	χ^2	P	Risk ratio
Tumour residue after resection	1.7030	0.5787	8.6593	0.0033	5.490 (1.766–17.070)
Bismuth type	0.9285	0.4042	5.2767	0.0216	2.531 (1.146–5.589)
Lymph node involvement (N)	0.7658	0.2698	8.0547	0.0045	2.151 (1.267–3.650)
Histological grade (G)	0.8493	0.3976	4.5626	0.0327	2.338 (1.073–5.096)

Values in parentheses are 95 per cent confidence intervals. Model $\chi^2 = 52.439$ ($P = 0.0001$)

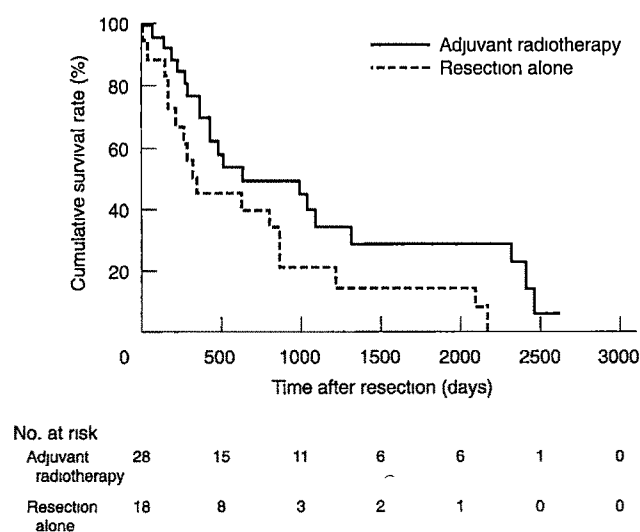


Fig. 3 Survival curves after adjuvant radiotherapy to microscopic residue after R₁ radical resection for patients with stage IVA disease. $P = 0.0138$ (log rank test)

193 days respectively. As of March 31 1999, 22 per cent of the patients ($n = 22$) were alive after resection; the overall 5-year cumulative survival rate and median survival time were 28 per cent and 624 days respectively. Nineteen patients survived more than 5 years, two, six, one and ten patients with stage I, II, III and IVA disease respectively. Of these 5-year survivors, six patients who underwent R₁ resection were treated by adjuvant radiotherapy.

Univariate analysis revealed that survival was significantly related to ten factors: performance status and jaundice (less than $162.5 \mu\text{mol/l}$), tumour localization and gross tumour appearance (polypoid *versus* non-polypoid), histopathological grade, T, N and M categories of the TNM system (Table 4), TNM stage grouping (Fig. 1) and residual tumour (Fig. 2). Survival was not significantly related to age (less than 64 *versus* 64 or more years; $P = 0.5008$), sex ($P = 0.5205$) and resection procedure (with hepatectomy ($n = 59$) *versus* without hepatectomy ($n = 42$); $P = 0.7435$). There were significant differences in the distribution of disease stages between R₀ and R₁ groups. Of the R₀ group, ten of 14 patients had

early stage I and II disease and two had stage IVA disease. In contrast, 52 (75 per cent) of 69 patients in the R₁ group had stage IV disease (IVA, *n* = 46; IVB, *n* = 6) and 12 (17 per cent) had early stage I or II disease. The majority (62 per cent, *n* = 63) of the patients who had resection had well differentiated adenocarcinoma (G₁). These patients had a 5-year survival rate of 38 per cent and a median survival of 971 days. On the other hand, the longest survival time among patients with moderately differentiated (G₂), poorly differentiated (G₃) and undifferentiated (G₄) carcinoma was 4.6 years, 3.7 years and 119 days respectively (Table 4).

Multivariate analysis of the 13 factors revealed that tumour location, histological grade, N and the level of residual tumour were significant independent prognostic factors. The factors leading to the greatest risk were residual tumour, tumour location, N and histological grade, for which the risk ratios were 5.490, 2.531, 2.151 and 2.338 respectively (Table 5).

The survival rates of patients with R₁ resection of stage IVA disease who received radiotherapy (*n* = 28) were significantly higher than those of patients who had resection alone (*n* = 18). The 5-year survival rate and median survival time were 34 per cent and 971 days in the former group, and 14 per cent and 290 days in the latter group (Fig. 3). However, there was no statistical improvement in survival by adjuvant radiotherapy for patients who had macroscopic residual disease of stage IVA tumour (*n* = 14).

Discussion

This study suggests that the performance status may be a good indicator of insidiously advanced disease, which should aid the surgeon in avoiding invasive procedures. Several reports have indicated that the preoperative bilirubin level may be an important risk factor for operative death and morbidity⁸⁻¹⁰. However, only one report has demonstrated this measurement to be a predictor of long-term survival¹¹. Since the preoperative bilirubin level may also be affected by biliary infection, preoperative percutaneous transhepatic drainage may be indicated for patients with a bilirubin level greater than 162.5 µmol/l. This would not only control the biliary infection but would also clearly outline the limit of tumour extension into the hepatic duct.

Cholangiographic localization and gross appearance of the tumour were found to be important prognostic factors. As shown in previous studies, patients with polypoid tumours had better survival than those with non-polypoid tumours¹²⁻¹⁴. Despite better prognosis of polypoid tumours, clinicians must still look for multiple tumour growth¹⁵ and delayed distant metastasis. In the present series, three of the eight patients with polypoid tumours had multiple polypoid tumours in the intrahepatic bile ducts and

multiple pulmonary metastases 6.1, 5.6 and 3.7 years after radical resection.

Although it was difficult to determine the limit of tumour extension into the hepatic ducts by preoperative diagnostic imaging and by exploration during the operation, the Bismuth type of the tumour localization aided in selecting resection procedures. Multivariate analysis revealed that Bismuth type was an independent prognostic factor. This analysis also revealed that the resection procedure, whether hepatectomy was added to bile duct resection, was not a significant prognostic factor. Consequently, the Bismuth type may be a useful preoperative diagnostic criterion for deciding the need for resection, the scope of resection and the type of hepatectomy to perform.

As reported previously^{11,16}, grade, T, N and M categories individually and TNM stage grouping influenced patient survival, contrary to the findings of the Hannover Medical School¹⁷.

The present curative resection rate after radical resection (*n* = 98) was lower (14 per cent) and the non-curative resection rate was higher (70 per cent) than rates published in recent reports^{11,16,18-22}. However, the survival rates after both curative and non-curative resections were better than those of others. One possible explanation for this may be differences in the distribution of patients in the T category. Klempnauer *et al.*¹⁶ reported a significantly higher incidence of T₁ or T₂ tumours (46 per cent; 62 of 136) than that in the present patient group (32 per cent; 32 of 101), which may explain why the curative resection rate in Klempnauer's study was higher.

The efficacy of adjuvant radiotherapy for bile duct carcinoma^{5,23-30} remains controversial. Pitt *et al.*³¹ reported that postoperative radiotherapy for patients with hilar cholangiocarcinoma did not improve survival. On the other hand, among patients with stage IVA disease in this study adjuvant radiotherapy for patients with R₁ resections significantly prolonged survival compared with resection alone. However, for patients with R₂ and R₀ resections adjuvant radiotherapy did not improve survival.

Several methods were used to predict the existence of microscopic tumour residue in the surgical margins, including the cholangiography, narrowing of the bile duct and tumour localization. When cholangiography demonstrated constriction of the bile duct, adjuvant radiotherapy was usually planned because this is an indication of severe invasion of tumour into the surrounding tissues of the bile duct, as reported previously¹². On the other hand, when cholangiography demonstrated papillary protuberance, adjuvant radiotherapy was not considered because this is an indication of a low incidence of cancer invasion beyond the fibromuscular connective tissue of the hepatic ducts¹².

To achieve complete tumour removal, the lymph nodes must also be resected carefully. Although the dissection of nodes in the hepatoduodenal ligament (N_1) for patients with T_1 tumour is not necessary, owing to the difficulty in distinguishing between T_1 and T_2 during surgery, this procedure was advocated in all patients. Six of the 28 patients with T_2 tumours and 26 of the 69 patients with T_3 lesions had metastases not only in N_1 but also beyond N_2 (peripancreatic, periduodenal, periportal, coeliac, and/or superior mesenteric and/or posterior pancreaticoduodenal nodes) (Table 3). Consequently, patients with T_2/T_3 disease must undergo lymphadenectomy of N_1 and N_2 nodes. Furthermore, patients with T_3 tumours must have the para-aortic nodes dissected in order to achieve complete removal of the tumour.

Given the impracticality of randomized clinical trials, these results and those of others clearly indicate that radical resection will improve the long-term survival of patients with main hepatic duct carcinoma. Patients with Bismuth type I or II lesions will do well following bile duct resection even if hepatectomy is not included in the resection. Combining radiation therapy with complete gross resection in locally advanced disease will improve survival with acceptable mortality and morbidity rates.

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Influence of allograft size to recipient body-weight ratio on the long-term outcome of renal transplantation

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Background: The critical nephron mass needed to meet the metabolic demands of an individual depends on the body-weight. This study evaluated the effect of the kidney transplant ultrasonographic size to recipient body-weight ratio (Tx/W) on the outcome of kidney transplantation.

Methods: A consecutive series of 104 cadaveric renal transplants was studied. Transplant cross-sectional area (TXSA) was measured ultrasonographically in the first week after transplantation as an index of renal size. A 'nephron dose' index (Tx/W) was calculated by dividing TXSA by recipient weight and was used to define three groups of patients, with high (more than 0.45), medium (0.3–0.45) or low (less than 0.3) Tx/W ratios. Isotope glomerular filtration rate (GFR) measurements were made at 1, 6 and 12 months after transplantation.

Results: The serum creatinine level was significantly lower in the first 5 years after transplantation in patients with a high Tx/W ratio than in those with a medium or low ratio. GFR measurements were marginally higher in the groups with a high and medium Tx/W ratio compared with the low Tx/W group. A statistically significant association between Tx/W ratio and graft survival was not found.

Conclusion: The renal transplant size to recipient weight ratio was an important determinant of long-term renal allograft function in this study. Extreme mismatching between allograft and recipient size should be avoided where possible, but the findings presented require confirmation in larger studies before clear recommendations can be made about size matching and kidney allocation.

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Introduction

Brenner *et al.*¹ have proposed the hypothesis that a deficient functioning renal mass leads to progressive renal injury owing to the detrimental effects of glomerular hyperfiltration. The theoretical sequence of events is that hyperfiltration leads to glomerular damage that sets in place a vicious cycle of further reduction in renal mass followed by ever worsening hyperfiltration². This mechanism may be particularly important in a transplanted kidney; the initial nephron mass is provided by a single kidney which may then lose nephrons as a result of episodes of acute rejection and the use of nephrotoxic immunosuppressive drugs³. The critical nephron mass needed to meet the metabolic demands within an individual depends on the body-weight⁴. Moreover, the number of nephrons in human kidneys has been shown to be quite variable, with a mean of approximately 600 000 per kidney and a standard deviation of over 200 000^{5–7}. This raises the possibility that renal transplantation may result in nephron underdosing, for example when a relatively small kidney is transplanted into

a relatively large recipient who has a greater metabolic demand for renal mass.

Indirect evidence suggests that renal mass is an important determinant of transplant outcome. Kidney transplants from female donors to male recipients fare worse than the male donor to female recipient combination^{3,4}. One possible explanation for this difference is a nephron mass effect; kidneys in women weigh 10–20 per cent less than those in men and have proportionately fewer glomeruli⁷. Nephron number cannot be measured in the living but kidney weight appears to be the best surrogate marker⁷. Unfortunately, it has not been routine clinical practice to weigh kidneys before transplantation and there are currently insufficient data to be certain about the effects of allograft size on the outcome of kidney transplantation. Serial ultrasonographic measurements of transplant size have been performed routinely in Leicester over many years. The aim of this study was to examine the influence of renal allograft ultrasonographic size to recipient body-weight ratio on the outcome of transplantation.

Patients and methods

A consecutive series of 104 heart-beating donor cadaveric renal transplants immunosuppressed with cyclosporin was studied. Grafts with primary non-function ($n=4$) were excluded, leaving 100 transplants under study. Patients were transplanted between 1989 and 1991, allowing relatively long-term follow-up. It has been routine practice in Leicester to perform serial ultrasonographic measurements of kidney transplant size. These measurements were used to monitor for the swelling associated with acute rejection^{8,9}. In the present study the scans performed in the first week after transplantation were used as a baseline estimate of the size of each transplanted kidney. After orientation of the longitudinal and transverse axes of the transplanted kidney, the ultrasound probe was positioned to demonstrate the largest hilar transverse cross-section. The real-time image was frozen and a hand-guided cursor was used to trace the outline of the renal capsule; from this the machine software calculated the hilar cross-sectional area (TXSA) in square centimetres. Three measurements of TXSA were made; the mean value was recorded and used in subsequent analyses. Previous studies involving several hundred renal allograft recipients have shown that this method of measurement has very high reproducibility with a coefficient of variation of less than 5 per cent^{9,10}. Preoperative patient weights (W) were recorded in kilograms and the kidney transplant ultrasonographic size to recipient body-weight ratio (Tx/W) was calculated as an index of nephron dose.

Immunosuppression

Immunosuppression was by cyclosporin given as part of a dual regimen with steroids, or a triple regimen with steroids and azathioprine. In the dual regimen, cyclosporin was given at an initial dose of 17 mg per kg per day and reduced to a baseline level of 7 mg per kg per day by 6 weeks after transplantation. Steroids were given orally as prednisolone at a starting dose of 100 mg/day reducing to 40 mg by the first week and 10 mg on alternate days by 6 months after transplantation. In the triple regimen, cyclosporin was administered at an initial dose of 10 mg per kg per day reducing to 5 mg per kg per day at 6 weeks after transplantation. The steroid regimen was the same and azathioprine was given at a dose of 1–2 mg per kg per day and adjusted according to the total white cell count.

Monitoring

All patients were followed up in the transplant clinic and renal function was determined by regular serum creatinine measurements. In addition, glomerular filtration rate (GFR) was determined using a single-shot chromium-51

ethylenediamine tetra-acetic acid isotope clearance technique. The GFR measurements were made at 1, 6 and 12 months after transplantation.

Clinical variables

The following were recorded at the time of transplantation: age, sex and weight of the recipient, number of previous transplants, number of human leucocyte antigen (HLA) DR mismatches, panel reactive antibody status, donor age and sex, first warm time, anastomosis time and cold ischaemic time. Delayed allograft function was defined as the need for dialysis in the first 7 days after transplantation excluding a single dialysis session in the immediate postoperative period performed specifically to treat a high serum potassium level. Acute allograft rejection was diagnosed clinically as the need for antirejection treatment with high-dose steroids, OKT3 or antithymocyte globulin, but was confirmed in all cases by needle-core biopsy.

Data analysis

Patients were divided into quartiles according to their Tx/W ratio. Three groups were then defined for comparison: high Tx/W ratio above 0.45 (upper quartile group; $n=20$), medium Tx/W ratio of 0.3–0.45 (interquartile group; $n=61$) and low Tx/W ratio of less than 0.3 (lower quartile group; $n=19$). Results were expressed as mean (s.e.m.). Continuous variables were compared using the Students' *t* test or Mann–Whitney *U* test as appropriate, and discrete variables were compared using Fisher's exact test. Graft survival was determined by the construction of Kaplan–Meier survival curves and the log rank test was used to compare differences between groups. All *P* values were two-tailed and $P < 0.05$ was considered significant.

Results

Patients in the three Tx/W ratio groups were well matched for age and sex, number of previous transplants, number of HLA-DR mismatches, panel reactive antibody status, donor age and sex, and ischaemic times (*Table 1*). Although there were more female recipients in the high Tx/W ratio group than in the low Tx/W ratio group, the differences did not reach statistical significance ($P=0.11$).

There was a progressive increase in transplant ultrasonographic size through the low, medium and high Tx/W groups, with statistically significant differences between all three groups. Recipient body-weight was significantly lower in the high Tx/W than in the low Tx/W group. At 1 year after transplantation, recipient body-weight had increased by approximately 2 kg in all three groups but was stable thereafter.

Table 1 Patient risk factors

	Tx/W ratio		
	Low (n=19)	Medium (n=61)	High (n=20)
Recipient sex ratio (M:F)	13:6	38:23	8:12
Recipient age (years)*	42(10)	43(12)	45(14)
Donor sex ratio (M:F)	9:10	34:27	11:9
Donor age (years)*	36(12)	37(12)	39(14)
Retransplants	2	7	1
HLA-DR mismatch*	0.9(0.6)	1.0(0.7)	1.0(0.6)
Panel reactive antibodies > 75%	0	2	1
Cold ischaemic time (h)*	20(5)	18(4)	19(5)
Anastomosis time (h)*	31(7)	30(5)	33(8)
Transplant ultrasonographic size (cm ²)*	20.3(2.9)	24.7(3.8)†	28.7(3.2)†§
Recipient weight (kg)*	70.5(12.8)	67.2(11.3)	61.8(10.1)‡

*Values are mean(s.d.). Tx/W, kidney transplant ultrasonographic size to recipient body-weight; HLA, human leucocyte antigen. † $P < 0.0001$, ‡ $P < 0.05$ versus low Tx/W ratio, § $P < 0.0001$ versus medium Tx/W ratio (Student's *t* test)

Table 2 Early graft function and rejection rates

	Tx/W ratio		
	Low (n=19)	Medium (n=61)	High (n=20)
Delayed graft function*	6 (32)	18 (30)	4 (20)
Acute rejection†	7 (37)	24 (39)	9 (45)

Values in parentheses are percentages. *Need for dialysis in first week after transplantation; †all confirmed by needle-core biopsy. Tx/W, kidney transplant ultrasonographic size to recipient body-weight

Early graft function and rejection rates (Table 2)

There were no significant differences between the three groups in the incidence of delayed graft function and biopsy-proven acute rejection in the first 3 months after transplantation.

Renal function (Figs 1 and 2)

The serum creatinine level was significantly lower in the first 5 years after transplantation in patients with a high Tx/W ratio than in those with a low or medium Tx/W ratio. Recipients with a low Tx/W ratio had an increasing serum creatinine level over the first 3 years. A lower mean serum creatinine level was seen in the group of patients with a low Tx/W ratio whose grafts functioned for 5 years. This effect was due to removal from the data set of patients with a high creatinine level whose grafts failed between years 3 and 5. Stable serum creatinine profiles over the first 5 years were

recorded in the groups with a medium and high Tx/W ratio (Fig. 1).

Isotope GFR measurements were higher in the groups with a high or medium Tx/W ratio than in the low Tx/W ratio group, but these differences did not reach statistical significance ($P = 0.12$). There were no significant differences in GFR between the groups with a medium and high Tx/W ratio in the first 12 months after transplantation.

Graft survival (Fig. 3)

Five-year allograft survival rates in the high, medium and low Tx/W ratio groups were 88, 71 and 74 per cent respectively ($P = 0.27$; log rank test).

Discussion

The principal finding of this study is that transplantation of a large kidney into a relatively smaller recipient results in better long-term renal function than transplantation of a small kidney into a relatively large recipient. These results suggest that renal allograft size is an important non-immunological determinant of outcome in renal transplantation.

In the present study, ultrasonographic measurements of renal cross-sectional area were used as an index of renal size. Although ultrasonographic imaging has been shown to be a reproducible method of measuring renal volume¹¹, it is accepted that the methods used here provide only an indirect measurement of renal size; there are no data on the relationship between ultrasonographic size and renal weight or number of glomeruli. Previous analyses have demonstrated a high degree of reproducibility for such

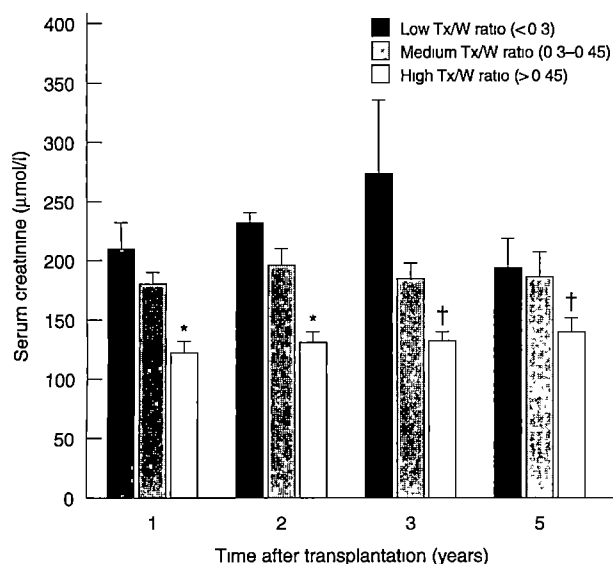


Fig. 1 Effect of kidney transplant ultrasonographic size to recipient body-weight (Tx/W) ratio on serum creatinine level. Values are mean(s.e.m.). * $P < 0.02$, † $P < 0.05$ versus low and medium Tx/W ratio (Student's t test)

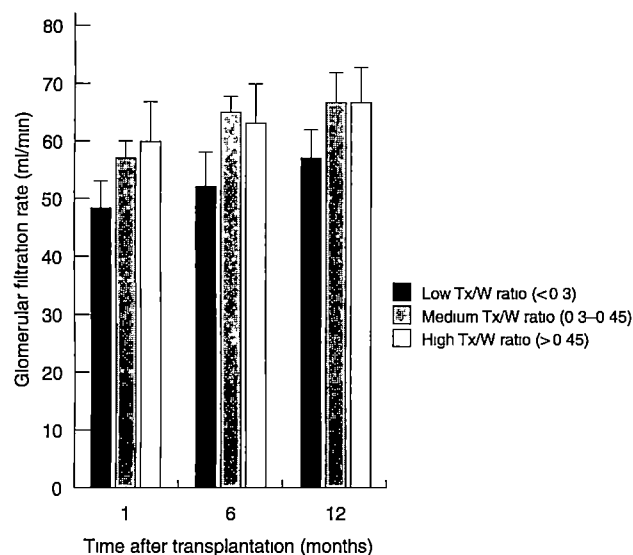


Fig. 2 Effect of kidney transplant ultrasonographic size to recipient body-weight (Tx/W) ratio on transplant glomerular filtration rate. Values are mean(s.e.m.)

measurements; as they were all performed by the same ultrasonographer in the present study, potential artefacts arising from interobserver errors were avoided. An attempt was made to reduce intraobserver error by repeating each measurement three times.

As serum creatinine is related to muscle mass, it is important to be sure that the Tx/W ratio calculated was not

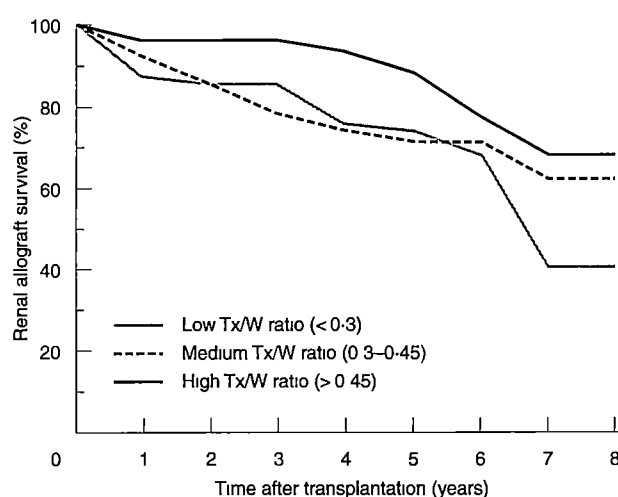


Fig. 3 Effect of kidney transplant ultrasonographic size to recipient body-weight (Tx/W) ratio on allograft survival. $P = 0.27$ (log rank test)

simply a surrogate marker of body-weight. The raw data presented in Table 1 show that there were no significant differences in recipient body-weight between low versus medium and medium versus high Tx/W groups. In contrast, kidney ultrasonographic size increased progressively through the three study groups, suggesting that this was the more dominant determinant of the Tx/W ratio. The differences in renal function between the three study groups were therefore unlikely to be simply a reflection of differences in body-weight and muscle mass. Furthermore, the rising serum creatinine concentration in the low Tx/W group occurred during a period in which the recipient body-weight was stable.

There is no satisfactory means of assessing nephron number in the living and therefore direct evidence to support or disprove Brenner's hypothesis concerning nephron underdosing¹ cannot be obtained. Kidney weight appears to be the best surrogate marker of nephron number⁷ and studies addressing the relationship between the graft weight to recipient body-weight ratio and renal transplant outcome have been reported^{12,13}. The preliminary analysis reported by Roth *et al.*¹² demonstrated a 3-year graft survival rate of greater than 70 per cent when the kidney to recipient body-weight (KW/BW) ratio was greater than 3.5 g/kg compared with a 3-year graft survival rate of less than 50 per cent when the ratio was less than 2 g/kg. Kim *et al.*¹³ studied the KW/BW ratio in 96 adult live donor transplants and found a small but statistically significant increase in serum creatinine 1 year after transplantation when the KW/BW ratio was less than 3.5 g/kg (mean serum creatinine 115 μmol/l) compared with more than 3.5 g/kg (mean serum creatinine 97 μmol/l). Graft survival data were not presented by these authors.

Other studies in humans have used a number of different indirect indices of renal mass. Donor to recipient body-weight ratio was not predictive of renal function or allograft survival in a retrospective analysis of 112 first cadaver kidney transplant recipients immunosuppressed with cyclosporin¹⁴. The authors also used data previously published by Nyengaard and Bendtsen⁷ to show that there was no correlation between total body-weight and kidney weight and did not necessarily reject the nephron underdosing hypothesis as a cause of chronic allograft dysfunction. In contrast, in the multivariate analysis presented by Eschwege *et al.*¹⁵, donor to recipient weight ratio was found to be an independent predictor of renal allograft function assessed by serum creatinine measurement 2 years after transplantation.

Body surface area (BSA) has also been used as a surrogate measurement of both metabolic demand and nephron mass. Gaston *et al.*¹⁶ reported that donor to recipient BSA ratio was not related to graft survival or kidney function over the first 5 years. This findings was contradicted in a similar study performed by Moreso *et al.*¹⁷. The latter study minimized the effect of donor factors by selecting 146 pairs of recipient kidneys received from the same donor. Recipient BSA was found to be an independent predictor of serum creatinine level 1 year after transplantation but the authors did not find an association between recipient BSA and graft survival. Of particular note in this study was the fact that differences in recipient BSA of as little as 10 per cent were found to influence the outcome of renal transplantation.

The present study demonstrated a trend towards improved graft survival in recipients with a high Tx/W ratio, but this did not reach statistical significance. Renal allograft survival is affected by a number of factors that may be interrelated and have non-linear effects. In view of this, and despite the fact that long-term follow-up data were available, the relatively small number of patients analysed may have been insufficient to demonstrate a more convincing association between transplant size and graft survival. This is consistent with the findings of several other studies in humans^{14,16,17}. Donor age is known to have an important influence on the outcome of kidney transplantation¹⁸, and may be an indicator of functioning renal mass. The three study groups were, however, well matched for this variable.

The data presented suggest an association between kidney allograft size to recipient weight ratio and the long-term outcome of renal transplantation. There is, however, considerable disagreement in the literature and larger studies that use allograft weight as a measure of the number of glomeruli are required to confirm the relationship. These would be facilitated by weighing every kidney before transplantation and recording this information on a

central database, such as the one held by the United Kingdom Transplant Support Service Authority. Currently, kidney allografts are allocated using HLA matching criteria, but transplant surgeons do take other factors such as donor age into account. Extreme mismatching between allograft and recipient size should be avoided where possible, but the available information is not clear enough to make stronger recommendations about size matching and kidney allocation.

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Carotid duplex imaging: variation and validation

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Background: Duplex imaging is increasingly used as the only investigation before carotid endarterectomy, but many different criteria exist in the literature for the detection of a severe (70–99 per cent) carotid stenosis. This study aimed to investigate current practice in carotid duplex imaging in Great Britain and Ireland.

Methods: A postal questionnaire was sent to 86 vascular surgical units.

Results: The median number of scans performed per year was 450 (range 60–4500). Thirty-six per cent of units who responded used peak systolic: end diastolic velocity ratio to calculate carotid stenosis. Overall, nine different major duplex criteria were used to grade carotid stenosis in 14 different systems of percentage bands. Only 51 per cent of units verified their duplex criteria against angiography. Eighteen per cent of units used two or more different types of duplex scanner and applied the same diagnostic criteria to each machine.

Conclusion: A wide variation in diagnostic duplex criteria and methods of grading stenosis exists among vascular units. Internal validation is not performed routinely. Standardization of duplex criteria would ensure greater consistency, but would not replace the need for validation of results within each unit.

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Introduction

The use of duplex ultrasonography for screening of internal carotid artery stenosis has increased¹. The safety of carotid endarterectomy without preoperative angiography has been demonstrated. Angiography can be performed selectively². Criticism of this policy arises from the variability in velocity criteria for defining carotid stenosis^{3–5}, and from variability between different duplex scanners which may cause significant variance in results^{6–8}. Operator experience and ability are also important factors in the variability of results^{8,9}. This study examined current practice regarding carotid duplex imaging, with particular reference to diagnostic criteria and their validation.

Materials and methods

A questionnaire on carotid duplex practice was sent to 86 vascular units identified from the membership of the Vascular Surgical Society of Great Britain and Ireland. Questionnaires were sent to units with two or more vascular surgeons who performed carotid endarterectomy. Twenty-seven teaching hospital units (31 per cent) and 59 district general hospital units (69 per cent) were surveyed. The questions were not aimed specifically at practice for patients

with stenosis greater than 70 per cent, but concerned all carotid duplex scans.

Results

Responses were received from 73 (85 per cent) of 86 units. The median number of scans performed yearly in each unit was 450 (range 60–4500). Almost half (48 per cent) of these scans were carried out in a vascular laboratory overseen by vascular surgeons. One-third (34 per cent) were performed in the radiology department.

The median number of people involved in carotid duplex imaging in each unit was 4 (range 1–10). Eight different disciplines performed scans. Imaging was performed most frequently by radiologists (34 per cent), vascular technologists (31 per cent) or medical physicists (28 per cent).

Eight units (11 per cent) always used another imaging modality to confirm duplex findings and 12 units (16 per cent) usually did. The majority (51 units; 70 per cent) performed other investigations only if the duplex scan was non-diagnostic. Intra-arterial or intravenous digital subtraction angiography was the commonest additional investigation performed (60 units); 17 units used magnetic resonance angiography. Some units used more than one additional investigation.

Eleven different makes of duplex scanner were used. Thirteen units (18 per cent) used more than one make of scanner and applied the same diagnostic criteria to each duplex scanner within the unit.

Diagnostic criteria

A number of different duplex criteria were used to categorize carotid stenoses (Table 1). Twenty-six (36 per cent) of 73 units used frequency shift or velocity readings only, while the remainder used differing ratios of peak systolic velocity or end-diastolic velocity readings in the internal carotid or common carotid arteries. These criteria were devised 'in house' in 12 units (16 per cent). Of the

remainder, 56 units (77 per cent) used criteria adopted either from the literature or from other units. Five units (7 per cent) did not state how their criteria were devised.

Only 37 (51 per cent) of the 73 units who replied validated their duplex criteria against angiography within their unit. Others used criteria that had been compared with angiography in the literature (19 of 73; 26 per cent) or in another unit (seven of 73; 10 per cent). Ten units had not validated their results against angiography ($n = 5$) or did not know whether this comparison had been performed ($n = 5$). Of 63 units whose duplex criteria were in some way validated against angiography, the angiograms were measured using North American methods in 18 units (29 per cent) and by European methods in 17 (27 per cent). The remaining 44 per cent (28 units) did not know which angiographic measurement method was used (23 of 63; 37 per cent) or did not answer (five of 63; 8 per cent).

Duplex criteria were used to categorize internal carotid artery disease into a variety of different bands of stenosis (Table 2). One-third of units used banding that simply categorized stenoses as above or below 70 per cent, with additional identification of occlusions. Eighteen units (25 per cent) did not have a cut-off at 70 or 75 per cent in their stenosis bands. These units could not have provided clinically relevant carotid duplex reports based on the original recommendation of a 70 per cent or greater stenosis as benefiting from carotid endarterectomy.

Table 1 Frequency of use of the various duplex diagnostic criteria

Duplex criteria	No. of units ($n = 73$)
Frequency shift	7 (10)
Velocity	19 (26)
PSVIC: EDVIC	26 (36)
PSVIC: PSVCC	13 (18)
PSVIC: EDVCC	1 (1)
All three ratios above	1 (1)
PSVIC: EDVIC and PSVIC: PSVCC	4 (5)
PSVIC: PSVCC and EDVIC: EDVCC	1 (1)
PSVIC: EDVCC	1 (1)

Values in parentheses are percentages PSVIC, internal carotid peak systolic velocity; EDVIC, internal carotid end-diastolic velocity; PSVCC, common carotid peak systolic velocity; EDVCC, common carotid end-diastolic velocity

Table 2 Variation in percentage bands of carotid stenosis used for reports in the different vascular units

Duplex-derived bands of carotid stenosis (%)	No. of units ($n = 73$)
No bands (actual stenosis only)	5 (7)
20–49, 50–79, 80–99 (Strandness)	17 (23)
<70, 70–99	26 (36)
10% bands above 50%	6 (8)
50–70, 70–90, >90	4 (5)
30–69, 70–90, 91–99	4 (5)
50–75, >75, >90	3 (4)
50–75, 75–95	2 (3)
50–75, >75, >90, 99	1 (1)
>70, 70–79, 80–90, >90	1 (1)
50–75, >75, >90, >95	1 (1)
50–75, >75, 80–90, >90	1 (1)
50–85, >85	1 (1)
50–69, 70–80, 80–99	1 (1)

All units included a separate category for occlusion

Discussion

This survey demonstrated a considerable diversity in approaches to carotid duplex imaging. There was no uniformity of criteria used to establish the degree of internal carotid artery stenosis. From a bewildering variety of duplex criteria arose further confusion in the differing bands of stenosis reported.

It is likely that the questionnaire was completed by one individual on behalf of each unit. Duplex criteria in vascular laboratories tend to be standard, but where individual radiologists were performing carotid scans, each radiologist may have used different criteria or duplex machines. This factor will increase the variation. The diversity was also reflected in the approach to validation. Only 51 per cent of units had validated the accuracy of their carotid duplex imaging against angiography. The accuracy of carotid duplex should be confirmed by local audit^{9–11}.

Criteria for grading carotid stenosis were both machine and laboratory specific^{6–8}. Both velocity criteria and frequency shift criteria show marked differences between different duplex machines. The application of similar diagnostic criteria to different equipment is a potential source of inaccuracy and should be avoided. Despite this, 18

per cent of units in this survey used more than one make of scanner, but applied the same duplex criteria to each machine.

Updated results of the European Carotid Surgery Trial (ECST)¹² have resulted in a revision of the level of internal carotid artery stenosis above which surgery is beneficial. This revised threshold is at least 80 per cent, and may be as high as 90 per cent depending on age and sex. These final ECST data have been modelled to provide a risk profile for individual patients based on medical risk without surgery and risk of perioperative stroke or death¹³. One of the important factors in this risk-modelling strategy is grading of carotid stenosis into 10 per cent bands above 70 per cent. Scan reports describing a simple greater or less than 70 per cent cut-off are no longer acceptable. Many of the duplex criteria and grading systems in use do not provide the necessary accuracy. At the very least, criteria should be validated within the unit for the specific equipment within the laboratory.

Carotid duplex imaging is undoubtedly useful as a screening tool, but the need for greater accuracy may require patients considered for operation to have biplanar carotid angiography for accurate measurement of their stenosis. Although angiography carries a 1 per cent risk of stroke¹⁴, this has to be offset against the risk of stroke and death for patients undergoing unnecessary carotid endarterectomy. If carotid duplex imaging is to be maintained as the only investigation before carotid endarterectomy, duplex criteria need to be standardized, and rigorous local validation should be performed.

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Cost-effective carotid endarterectomy

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Background: Although carotid endarterectomy is increasing in the UK, there is evidence that the procedure is still underused. Methods of reducing cost in a single vascular unit have been assessed using a continuous audit including outcome measures.

Methods: A consecutive series of 333 patients admitted over 7 years under a single consultant surgeon were studied. Outcome measures included the rate of perioperative neurological complication of any kind, and death. The length of hospital stay and the number of readmissions within 30 days were recorded prospectively by computerized audit.

Results: Over the interval of the study, the number of preoperative investigations was reduced; angiography and cerebral computed tomography were reserved for specific indications. The median duration of hospital stay decreased from 7 to 2 days. There was no change in the stroke and death rate (3 per cent) during the study and only two patients required readmission within 30 days.

Conclusion: Carotid endarterectomy can be performed cost-effectively using non-invasive preoperative investigations for the majority of patients. In-hospital stay has been reduced and the routine use of intensive care replaced by a 2-h stay in theatre recovery. These changes have been achieved without compromising patient safety.

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Introduction

The publication of two large multicentre trials confirming the value of carotid endarterectomy has been followed by a large increase in the number of operations performed in the UK^{1,2}. There is, however, evidence that this operation is still underused, and many patients who would benefit are not being referred³. The potential number of patients for operation may increase further if the Asymptomatic Carotid Surgery Trial (ACST) shows a benefit for carotid endarterectomy⁴. It is unlikely that resources will be allocated to treat these extra patients, and therefore it is important to minimize the cost of the procedure. The efficacy of carotid endarterectomy is dependent on low complication rates; any change in the care of these patients must not affect morbidity or mortality rates. A continuous prospective audit of investigations and outcome from carotid surgery has been performed over 7 years, during which the number of preoperative investigations and the duration of post-operative stay, together with outcome, have been studied.

Patients and methods

All patients undergoing carotid endarterectomy under the care of a single vascular surgeon since 1992 were entered

prospectively on a computerized vascular database. Patients were assessed by the vascular surgeon in the outpatient department, and any with unusual or atypical features were also assessed by a neurologist. All cases were discussed both before and after operation at a regular neurovascular audit meeting attended by a vascular surgeon, neurologist, neuroradiologist and ultrasound technologist. The standard preoperative investigations performed in 1992 are shown in *Table 1*. The outcome measures in the audit were: the total perioperative neurological event rate, death within 30 days of operation, the duration of hospital stay and the number of readmissions within 30 days of discharge.

Table 1 Standard preoperative investigations before carotid endarterectomy (1992)

Full blood count, clotting screen, group and save serum
Urea and electrolytes, creatinine, glucose, lipid screen
Twelve-lead electrocardiography
Carotid artery colour flow duplex scan
Transcranial Doppler scan of the middle cerebral arteries
Carotid and cerebral digital subtraction angiography using aortic arch injection
Cerebral computed tomography

There were four indications for carotid endarterectomy. The majority were patients with a 70 per cent or greater symptomatic stenosis who had experienced a recent ipsilateral transient ischaemic attack (TIA) or non-disabling stroke ($n=267$). The other two categories were asymptomatic patients who were enrolled in the ACST⁴ ($n=14$), or who were due to have coronary artery bypass surgery ($n=17$); a further 35 asymptomatic patients were thought likely to benefit from surgery. General anaesthesia was used in all operations, which were performed either by the consultant or by a specialist registrar under supervision. Continuous intraoperative transcranial Doppler monitoring of the middle cerebral artery was routine, as was completion duplex imaging after arteriotomy closure, but before closure of the wound⁵. After operation patients were transferred to the intensive care unit (ICU) or recovery suite.

Routine preoperative computed tomography (CT) was discontinued during the study because the findings did not appear to alter patient management. In 1995, preoperative angiography was discontinued and replaced by duplex imaging, following an audit of the concordance between angiography and duplex imaging⁶. From 1993, patients were monitored after operation for 4 h in the surgical recovery area and were no longer sent routinely to the ICU for overnight observation. Monitoring was subsequently reduced to 2 h if there were no complications. On return to the ward, care was provided by the regular nurses; no patient had 'special' nursing care.

The estimated hospital costs (available as a result of department cross-charging) were: intensive care, £1500 per night; cerebral CT, £100; carotid angiography, £240 for an arch angiogram and £270 for selective carotid catheterization; carotid duplex and transcranial Doppler assessment, £100.

Results

From January 1992 to December 1998, 333 carotid endarterectomies were performed. The median age of the patients was 65 (range 41–84) years. The median duration of hospital stay decreased during the interval of study from 7 to 2 days (*Fig. 1*). The 2 days included the entire length of stay: most patients were admitted on the day before surgery and discharged on the day after operation. The reasons for delay are listed in *Table 2* for the last 267 patients who were treated after discharge on the first postoperative day became routine. Since this policy was adopted, only one patient has been admitted to the ICU following an on-table cardiac arrest, and five patients were delayed in theatre recovery for control of blood pressure. *Table 3* shows the outcome and results in 333 patients, together with complications and

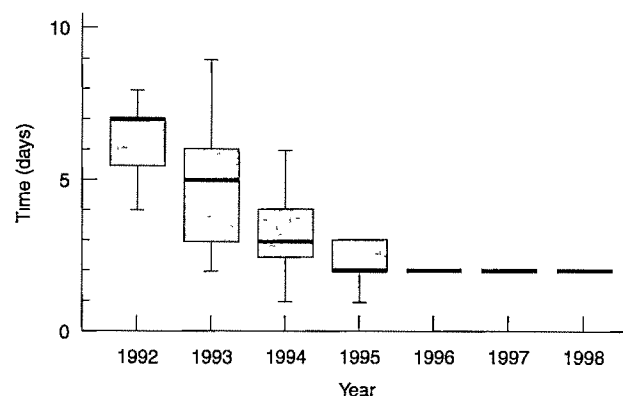


Fig. 1 Duration of hospital stay for carotid endarterectomy. Horizontal bars denote median values; box, interquartile range; whiskers, full range

Table 2 Reasons for delay in routine discharge on the first post-operative day after carotid endarterectomy for the last 267 patients

	No. of patients
Simultaneous coronary artery bypass	17
Social*	8
Control of blood pressure	5
Respiratory problems	5
Stroke	2
Urinary retention	1
Restarting oral anticoagulants	1
Discharge on day after operation	228 (85)
Total	267

Value in parenthesis is a percentage *Usually related to the distance home

potential cost saving. Three patients died, two from myocardial infarction and one from mesenteric ischaemia. Stroke affected eight patients, one of whom died from myocardial infarction. The overall stroke and death rate was therefore 3 per cent (ten patients). There was no significant change in complication rates during the study, even though an increasing number of operations were performed by trainees under consultant supervision. *Table 3* documents the estimated median cost saved per carotid endarterectomy for each year. This was calculated by adding the cost saved on investigations and intensive care for an average patient per year to the median length of stay for that year. Two patients required readmission within 30 days after discharge: one recovered following a stroke and the other died as a result of mesenteric ischaemia.

A survey by questionnaire was undertaken to assess whether early discharge on the first postoperative day was acceptable to the patients. A consecutive series of 50 patients was assessed by telephone or letter. The person

Table 3 Duration of hospital stay, complications of carotid endarterectomy and cost saving

Year	No. of patients	Median length of stay (days)	Death	Stroke	TIA	Other complications	Readmission within 30 days	Cost saving* (£)
1992	24	7	0 (0)	0 (0)	0 (0)	2 (8)	0 (0)	0
1993	35	5	0 (0)	3 (9)	1 (3)	2 (6)	0 (0)	1800
1994	35	3	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)	2100
1995	51	2	1 (2)	3 (6)	1 (2)	0 (0)	0 (0)	2490
1996	67	2	1 (1)	1 (1)	1 (1)	3 (4)	1 (1)	2550
1997	62	2	1 (2)	0 (0)	1 (2)	2 (3)	1 (2)	2610
1998	59	2	0 (0)	1 (2)	0 (0)	2 (3)	0 (0)	2630
Total	333		3 (1)	8 (2)	4 (1)	13 (4)	2 (1)	

TIA, transient ischaemic attack. *Method of calculation described in the text

administering the questionnaire was not involved in the patients' care in hospital. Forty-one of the 50 patients were happy to have been discharged on the first postoperative day. Nine patients were not discharged on the day after operation for the following reasons: two patients felt unsteady, one patient was worried that the wound would 'burst', one patient with pre-existing prostate problems had urinary frequency, one patient developed urinary retention and required catheterization (it is not policy to catheterize these patients routinely) and four gave no specific reason – they were simply 'not happy' to go home. Six of the 50 had contacted their general practitioner in the 4 weeks following discharge from hospital for advice regarding the operation.

Discussion

The management of patients having carotid endarterectomy can be divided into three phases: preoperative clinical assessment and investigation, operative management, and postoperative care. Satisfactory clinical results can be achieved only if each phase is performed appropriately. Preoperative assessment is aimed at confirming the indications for endarterectomy. Usually there are two tasks: first to confirm that the patient has had a focal neurological deficit, and second to image that carotid artery. If there is any doubt about the neurological symptoms, referral to a neurologist is helpful. In this unit, all asymptomatic patients, those with focal symptoms associated with less than 70 per cent stenosis and those with non-focal neurological symptoms, are referred for a neurological opinion. Carotid imaging is achieved by duplex ultrasonography, which in many centres is the sole method used to assess the degree of carotid stenosis⁶⁻⁹. Each centre should perform an audit, using an alternative imaging modality such as digital subtraction angiography or magnetic resonance angiography to establish the accuracy of local

ultrasonographic investigation⁶. Similarly, new personnel within an ultrasound department should be audited against more experienced staff, or a standard investigation.

Arguments in favour of performing angiography in addition to duplex imaging include an ability to detect aortic arch and proximal great vessel disease, as well as intracranial disease such as carotid syphon stenosis, intracerebral aneurysm and arteriovenous malformation. However, the incidence of these findings is low, and even when present they infrequently alter the management of a patient^{10,11}. Avoidance of angiography eliminates the risk of contrast medium reactions, neurological and local puncture site complications^{12,13}. The main indications for carotid angiography in this practice are to confirm occlusion of the internal carotid artery and to assess the degree of stenosis in the presence of heavy calcification¹⁴. Cerebral CT rarely alters the management of patients having carotid endarterectomy. The majority of patients who present with retinal symptoms or TIA have a normal CT finding^{15,16}. Patients who have recurrent TIAs affecting different territories should have CT and a neurological opinion before surgery is considered.

The avoidance of perioperative stroke is extremely important. Transcranial Doppler (TCD) monitoring of the middle cerebral artery is very useful in detecting particulate emboli that are disturbed during dissection of the carotid bifurcation¹⁷. TCD can also be used to detect low intracerebral flow, which may respond to the repositioning of a self-retaining retractor or the use of a shunt. Technical excellence and continuous irrigation to remove thrombotic debris are important in preventing perioperative carotid thrombosis and subsequent stroke¹⁸. High-resolution duplex imaging carried out after arteriotomy closure, but before wound closure, allows correction of significant defects before reversal of anaesthesia⁵.

The routine use of the ICU for early postoperative care has been questioned^{19,20}. All patients require close mon-

itoring in the early postoperative phase, but the majority do not require full intensive care. The most common complications are stroke, bleeding, and either hypotension or hypertension; these usually manifest themselves within 2 h after operation. If the blood pressure is difficult to control and/or inotropes are required, patients are usually kept in the recovery room overnight. Patients who are stable can be transferred to the ward after 2 h in the recovery area.

The duration of hospital stay after carotid endarterectomy is decreasing rapidly^{21–23}. The majority of patients are self-caring on the first postoperative day, and the use of absorbable subcutaneous sutures to close the wound removes the need for them to stay in hospital until the sutures or clips are removed. Cervical incisions heal well, and rarely give problems. Patients with neurological problems and those who require medication to control blood pressure require a longer hospital stay, but the majority of patients can be discharged on the first day. The present survey shows that this policy is acceptable to the majority of patients. Safety is confirmed by the low readmission rate.

Given careful clinical selection and high-quality validated ultrasonography, this study has shown that the routine use of preoperative angiography and CT are not justified before carotid endarterectomy. Recovery from surgery does not require monitoring in intensive care, but rather in the recovery room for 2 h. The majority of patients can be discharged on the first postoperative day. These changes can be achieved with acceptable morbidity and mortality rates, and with a low incidence of readmission²³.

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Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia

The Global Lower Extremity Amputation Study Group

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Background: This study was established to enable a comparison of lower extremity amputation incidence rates between different centres around the world.

Methods: Ten centres, all with populations greater than 200 000, in Japan, Taiwan, Spain, Italy, North America and England collected data on all amputations done between July 1995 and June 1997. Patients were identified from at least two data sources (to allow checks on ascertainment); denominator populations were based on census figures.

Results: The highest amputation rates were in the Navajo population (43.9 per 100 000 population per year for first major amputation in men) and the lowest in Madrid, Spain (2.8 per 100 000 per year). The incidence of amputation rose steeply with age; most amputations occurred in patients over 60 years. In most centres the incidence was higher in men than women and the incidence of major amputations was greater than that of minor amputations. Diabetes was associated with between 25 and 90 per cent of amputations.

Conclusion: Apart from the Navajo centre, differences in the known prevalence of diabetes could not account for the differences in overall incidence of amputation. Differences in the prevalence of peripheral vascular disease are likely to be important, but this and the role of other factors, including availability of health care, are worthy of further investigation.

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Introduction

This study was established to overcome some of the difficulties encountered in comparing amputation rates from previously published studies. For example, inconsistencies between published studies may relate to the inclusion or exclusion of people with diabetes in the overall rates, the inclusion of first ever, or all, amputations and differences in the level of amputation. In addition, age-specific rates tend not to be presented, making comparison between populations with different age structures difficult. Finally, different studies often use different data sources to identify amputations. It is therefore possible that differences exist in the level of ascertainment of amputations between studies¹.

The main aim of this study was to enable a comparison of the incidence of lower extremity amputations between populations by using a standard approach to data collection and analysis.

Materials and methods

Recruitment and characteristics of the study centres

Most centres were recruited to the study following publication of the study protocol¹. Other centres became involved once the study was established, mainly through professional contact with investigators at participating centres. A detailed 'Methods of Operation' manual was written and distributed to each centre.

Sufficient data were received from ten centres, in six countries. Three centres provided insufficient data for presentation here. Data were collected on all amputations occurring between 1 July 1995 and 30 June 1997. The names, population sizes and sources of data for amputations from each of the centres are shown in *Table 1*. To participate, each centre had to have access to up-to-date demographic data for their population, to allow the calculation of age- and sex-specific rates. Tochigi in Japan

Table 1 Participating centres, population size and sources from which amputations were identified

Centre	Population	Sources
Leeds, UK	732 055	Operating theatre records Hospital discharge data Limb fitting centre records
Leicester, UK	923 504	Operating theatre records Surgical records Hospital discharge data Diabetic foot clinic Other
Madrid, Area 7, Spain	569 307	Hospital records (Servicio de Cirugia Vascular) Theatre records Prescribing physicians
Middlesborough, UK	288 887	Operating theatre records Hospital discharge data Limb fitting centre records Diabetic foot register
Montgomery county, USA	705 179	Operating theatre records Hospital discharge data
Navajo area, IHS, USA	209 147	IHS hospital discharge data Operating theatre records Lower extremity amputation registries
Newcastle upon Tyne, UK	283 000	Operating theatre records Hospital discharge data Limb fitting centre records
Ilan, Taiwan	465 120	Hospital discharge data Limb fitting centre records Bureau of social welfare
Tochigi, Japan	1 982 565	Orthopaedic and surgical records Handicap register Physical therapist records
Vicenza, Italy	279 980	Hospital discharge data Operating theatre records Limb fitting centre records

IHS, Indian Health Service

was only able to collect data on first ever major and minor amputations.

Definition of lower extremity amputation and collection of data

The definition of a lower extremity amputation used in this study was the complete loss of any part of the lower limb, for any reason, in the following anatomical planes: in the transverse anatomical plane proximal to, and including, the subtalar joint and in the frontal anatomical plane distal to the subtalar joint. A major amputation was defined as through, or proximal to, the tarsometatarsal joint and a minor amputation as one distal to this joint.

Centres were asked to use more than one source to identify patients, ideally at least three, but where this was not possible, two were accepted. Sources from which patients were identified were dependent on local circumstances (*Table 1*). As far as possible, medical records were traced for each patient and a standard data abstraction form

was completed. With the exception of some aspects of personal details, the data abstraction form was identical for each of the centres. The data collected included the date and level of the most recent amputation, conditions associated with it (including diabetes, infection, peripheral vascular disease and trauma), and the presence and level of any previous amputations.

Centres undertook a pilot study to test the feasibility of abstracting data from the different sources, and sent the completed forms to Newcastle (the coordinating centre) in order to check that the data collection forms from each centre were completed to a comparable and adequate standard.

Data analysis

Most centres entered their data locally using a standard database format designed to allow only valid values for each variable. Age and sex denominator population sizes were taken from the most recent census figures for each

population. Age-specific, crude and age-adjusted rates are presented for men and women separately. As all the centres (with the exception of the Navajo area) have age structures with a relatively elderly population, the standard European population² was used for direct age standardization.

This study measured the incidence of amputations in whole geographically defined populations and not samples of larger populations, so confidence intervals or *P* values were not used. What is relevant is the level of ascertainment of amputations (i.e. whether all amputations occurring in the study populations were identified). Estimates of the level of ascertainment were derived using capture-recapture methods^{3,4}. These derive their name from their development and use in estimating the size of wildlife populations and have increasingly been used in epidemiology. With more than one source of patients, the total number can be estimated by contrasting the number identified from one source only and those identified from more than one source⁵. With only two sources the capture-recapture method is based on the assumption that the sources are independent. This assumption is rarely met with health care data, but if the direction of dependency is known it is still possible to derive useful information⁶. This approach has been used here where only two sources were available. With three or more sources log-linear modelling⁵ and a confidence interval for the total number of amputations can be computed using a method based on goodness of

fit⁷. The number of patients was too small to provide robust age-specific estimates of ascertainment, but it was felt important to examine ascertainment for first and all amputations separately, as experience suggested that ascertainment among these categories may differ. The ascertainment of minor and major amputations was also examined separately. Some sources, in particular limb fitting centres, provided data on major but not minor amputations. In order to have a reasonable number in each of these different categories in the analyses, men and women were combined.

Population prevalence figures for diabetes were not available for all centres, so the number of people with known diabetes are presented simply as a proportion of all lower extremity amputations in each centre. The proportions of patients with peripheral vascular disease, infection and trauma are also presented.

Results

Overall incidence of amputation

There were marked differences in the overall incidence of both first and all amputations between the study centres (Tables 2–5), with over a tenfold difference between the highest and lowest areas. Age-adjusted data for first ever major and minor amputations are illustrated in Figs 1 and 2.

Table 2 Age-specific, crude and age-adjusted (to a standard European population) incidence (number per 100 000 population per year) of first and all major amputations in men

Centre		Age group (years)					All	Age adjusted
		0–19	20–39	40–59	60–79	80+		
Leeds, UK	First	1.1 (2)	0.8 (2)	11.5 (20)	65.1 (70)	97.2 (17)	15.4 (111)	16.4
	All	1.1 (2)	0.8 (2)	15.0 (26)	80.0 (86)	108.6 (19)	18.8 (135)	19.9
Leicester, UK	First	0.0	0.0	3.9 (9)	22.3 (30)	40.0 (9)	5.2 (48)	5.6
	All	0.0	0.0	4.4 (10)	29.7 (40)	48.9 (11)	6.6 (61)	7.2
Madrid, Spain	First	0.0	0.0	0.8 (1)	9.8 (9)	35.3 (5)	2.9 (15)	2.8
	All	0.0	0.0	2.4 (3)	10.9 (10)	49.4 (7)	3.8 (20)	3.7
Middlesbrough, UK	First	0.0	2.4 (2)	14.7 (10)	84.1 (36)	77.9 (4)	18.4 (52)	19.8
	All	0.0	2.4 (2)	23.5 (16)	121.5 (52)	77.9 (4)	26.2 (74)	27.8
Montgomery, USA	First	0.0	0.0	14.7 (26)	84.9 (85)	79.4 (17)	18.8 (128)	19.2
	All	0.0	0.0	24.9 (44)	154.0 (154)	159.9 (34)	34.2 (232)	34.9
Navajo area, USA	First	1.0 (1)	3.2 (2)	34.8 (10)	184.6 (22)	176.8 (4)	18.9 (39)	43.9
	All	1.0 (1)	3.2 (2)	41.8 (12)	260.1 (31)	221.0 (5)	24.8 (51)	58.7
Newcastle, UK	First	1.4 (1)	1.0 (1)	14.9 (9)	61.9 (25)	78.1 (5)	14.8 (41)	16.3
	All	1.4 (1)	2.1 (2)	19.9 (12)	74.3 (30)	93.8 (6)	18.4 (51)	20.2
Ilan, Taiwan	First	0.7 (1)	4.2 (7)	6.1 (6)	32.8 (19)	37.9 (2)	7.2 (35)	9.2
	All	0.7 (1)	4.2 (7)	8.2 (8)	36.2 (21)	75.8 (4)	8.5 (41)	11.3
Tochigi, Japan	First	0.0	0.7 (4)	4.1 (24)	12.1 (38)	24.3 (10)	3.9 (76)	3.8
	All	—	—	—	—	—	—	—
Vicenza, Italy	First	0.0	0.0	8.1 (6)	17.4 (7)	75.5 (5)	6.6 (18)	6.9
	All	0.0	0.0	9.4 (7)	32.3 (13)	75.5 (5)	9.2 (25)	9.6

Values in parentheses are number of amputations observed over 2 years

Table 3 Age-specific, crude and age-adjusted (to a standard European population) incidence (number per 100 000 population per year) of first and all major amputations in women

Centre		Age group (years)					All	Age adjusted
		0-19	20-39	40-59	60-79	80+		
Leeds, UK	First	0.6 (1)	1.7 (4)	7.2 (12)	26.7 (34)	56.9 (23)	9.9 (74)	8.3
	All	0.6 (1)	1.7 (4)	8.4 (14)	34.6 (44)	69.3 (28)	12.2 (91)	10.2
Leicester, UK	First	0.0	0.7 (2)	0.9 (2)	17.0 (26)	23.2 (11)	4.5 (41)	3.8
	All	0.0	0.7 (2)	0.9 (2)	19.6 (30)	25.3 (12)	5.0 (46)	4.3
Madrid, Spain	First	0.0	0.0	0.0	2.1 (3)	5.8 (2)	0.8 (5)	0.5
	All	0.0	0.0	0.0	2.1 (3)	5.8 (2)	0.8 (5)	0.5
Middlesborough, UK	First	0.0	1.2 (1)	4.4 (3)	19.5 (10)	60.5 (8)	7.5 (22)	6.2
	All	0.0	1.2 (1)	5.8 (4)	29.2 (15)	68.1 (9)	9.8 (29)	8.4
Montgomery, USA	First	0.0	0.0	9.6 (18)	37.0 (48)	148.5 (62)	17.5 (128)	12.5
	All	0.0	0.0	15.6 (29)	49.4 (64)	186.8 (78)	23.4 (171)	17.0
Navajo area, USA	First	0.0	0.0	17.7 (6)	95.5 (14)	106.2 (3)	10.5 (23)	22.4
	All	0.0	0.0	17.7 (6)	136.4 (20)	212.5 (6)	14.7 (32)	32.0
Newcastle, UK	First	0.0	0.0	3.3 (2)	29.4 (15)	54.9 (9)	9.0 (26)	7.0
	All	0.0	1.1 (1)	5.0 (3)	31.4 (16)	79.3 (13)	11.4 (33)	8.8
Ilan, Taiwan	First	0.0	0.0	3.2 (3)	27.6 (14)	43.5 (3)	4.5 (20)	6.4
	All	0.0	0.0	3.2 (3)	31.6 (16)	87.0 (6)	5.6 (25)	8.3
Tochigi, Japan	First	0.0	0.0	1.1 (6)	4.4 (17)	7.5 (6)	1.5 (29)	1.2
	All	—	—	—	—	—	—	—
Vicenza, Italy	First	0.0	1.1 (1)	0.0	14.5 (8)	100.9 (16)	8.7 (25)	5.6
	All	0.0	1.1 (1)	0.0	20.0 (11)	119.9 (19)	10.8 (31)	7.0

Values in parentheses are number of amputations observed over 2 years

Table 4 Age-specific, crude and age-adjusted (to a standard European population) incidence (number per 100 000 population per year) of first ever and all minor amputations in men

Centre		Age group (years)					All	Age adjusted
		0-19	20-39	40-59	60-79	80+		
Leeds, UK	First	2.7 (5)	2.1 (5)	13.3 (23)	46.5 (50)	57.1 (10)	12.9 (93)	13.6
	All	3.8 (7)	2.9 (7)	17.9 (31)	80.0 (86)	91.4 (16)	20.4 (147)	21.5
Leicester, UK	First	0.0	0.4 (1)	3.0 (7)	6.7 (9)	13.3 (3)	2.2 (20)	2.3
	All	0.0	1.1 (3)	3.9 (9)	11.1 (15)	13.3 (3)	3.2 (30)	3.4
Madrid, Spain	First	0.0	0.0	4.0 (5)	6.5 (6)	14.1 (2)	2.5 (13)	2.4
	All	0.0	0.0	5.6 (7)	9.8 (9)	21.2 (3)	3.6 (19)	3.5
Middlesborough, UK	First	0.0	3.5 (3)	14.7 (10)	42.1 (18)	58.4 (3)	12.0 (34)	13.0
	All	0.0	3.5 (3)	17.7 (12)	65.4 (28)	58.4 (3)	16.3 (46)	17.4
Montgomery, USA	First	0.0	2.0 (5)	19.8 (35)	47.9 (48)	50.5 (11)	14.5 (99)	14.4
	All	0.0	5.0 (10)	30.1 (53)	88.0 (88)	56.2 (12)	24.0 (163)	24.3
Navajo area, USA	First	1.0 (1)	11.2 (7)	114.9 (33)	176.2 (21)	88.4 (2)	31.1 (64)	61.8
	All	1.0 (1)	20.9 (13)	174.0 (50)	293.6 (35)	132.6 (3)	49.5 (102)	98.8
Newcastle, UK	First	0.0	2.1 (2)	5.0 (3)	27.2 (11)	93.8 (6)	7.9 (22)	8.8
	All	0.0	2.1 (2)	14.9 (9)	44.6 (18)	109.4 (7)	13.0 (36)	14.4
Ilan, Taiwan	First	0.0	1.2 (2)	1.0 (1)	3.5 (2)	37.9 (2)	1.5 (7)	2.3
	All	0.0	1.2 (2)	1.0 (1)	5.2 (3)	37.9 (2)	1.9 (8)	2.5
Tochigi, Japan	First	0.2 (1)	0.0	0.7 (4)	1.3 (4)	4.9 (2)	0.6 (11)	0.6
	All	—	—	—	—	—	—	—
Vicenza, Italy	First	3.6 (2)	0.0	5.4 (4)	22.4 (9)	0.0	5.5 (15)	5.8
	All	3.6 (2)	0.0	8.1 (6)	39.8 (16)	0.0	8.8 (24)	9.2

Values in parentheses are number of amputations observed over 2 years

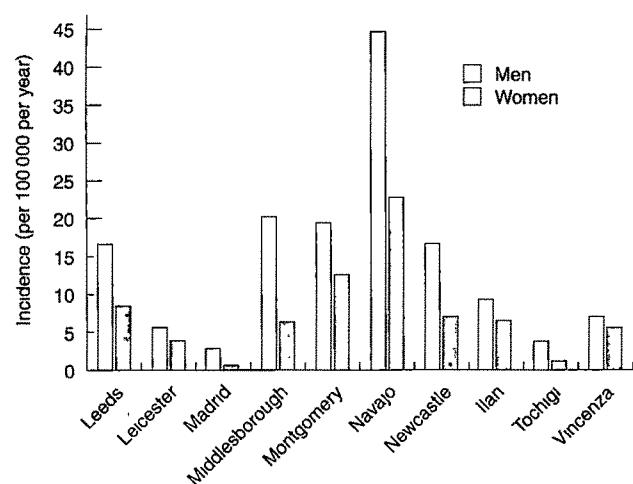
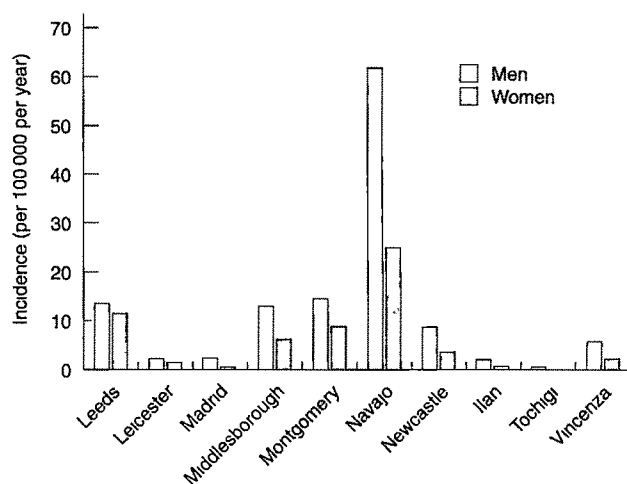
The highest rates for men and women, for first and all major and minor amputations, were in the Navajo area. The lowest rates for all first amputations were in the Japanese

population of Tochigi. Between the western European centres there were also marked differences. Rates in Madrid (Spain), Vicenza (Italy) and Leicester (UK) were substan-

Table 5 Age-specific, crude and age-adjusted (to a standard European population) incidence (number per 100 000 population per year) of first ever and all minor amputations in women

Centre		Age group (years)					All	Age adjusted
		0-19	20-39	40-59	60-79	80+		
Leeds, UK	First	2.8 (5)	3.0 (7)	12.6 (21)	33.0 (42)	54.5 (22)	13.0 (97)	11.5
	All	2.8 (5)	3.5 (8)	16.8 (28)	40.1 (51)	74.3 (30)	16.4 (122)	14.3
Leicester, UK	First	0.0	0.0	0.9 (2)	9.2 (14)	2.1 (1)	1.6 (17)	1.7
	All	0.0	0.0	0.9 (2)	9.8 (15)	2.1 (1)	2.0 (18)	1.8
Madrid, Spain	First	0.0	0.0	0.0	2.1 (3)	5.8 (2)	0.8 (5)	0.5
	All	0.0	0.0	0.0	2.1 (3)	5.8 (2)	0.8 (5)	0.5
Middlesborough, UK	First	1.3 (1)	1.2 (1)	4.4 (3)	21.4 (11)	37.8 (5)	7.1 (21)	6.2
	All	1.3 (1)	1.2 (1)	5.8 (4)	31.1 (16)	37.8 (5)	9.2 (27)	8.1
Montgomery, USA	First	0.0	0.0	12.9 (24)	30.8 (40)	26.3 (11)	10.3 (75)	8.7
	All	0.0	2.0 (4)	13.5 (25)	37.0 (48)	38.3 (16)	12.8 (93)	10.8
Navajo area, USA	First	3.0 (3)	0.0	29.6 (10)	102.3 (15)	35.4 (1)	13.3 (29)	25.1
	All	3.0 (3)	0.0	56.2 (19)	163.7 (24)	35.4 (1)	21.5 (47)	41.2
Newcastle, UK	First	1.4 (1)	1.1 (1)	1.7 (1)	15.7 (8)	18.3 (3)	4.9 (14)	4.1
	All	1.4 (1)	1.1 (1)	1.7 (1)	21.6 (11)	30.5 (5)	6.6 (19)	5.4
Ilan, Taiwan	First	0.7 (1)	0.0	0.0	4.0 (2)	14.5 (1)	0.9 (4)	1.2
	All	0.7 (1)	0.0	0.0	4.0 (2)	14.5 (1)	0.9 (4)	1.2
Tochigi, Japan	First	0.0	0.0	0.2 (1)	0.8 (3)	1.3 (1)	0.3 (5)	0.2
	All	—	—	—	—	—	—	—
Vicenza, Italy	First	0.0	0.0	2.7 (2)	7.3 (4)	12.6 (2)	2.8 (8)	2.2
	All	0.0	0.0	2.7 (2)	10.9 (6)	12.6 (2)	3.5 (10)	2.7

Values in parentheses are number of amputations observed over 2 years

**Fig. 1** Age-adjusted incidence of first ever major amputations (per 100 000 population per year)**Fig. 2** Age-adjusted incidence of first ever minor amputations (per 100 000 population per year)

tially lower than those in the north of England at Leeds, Middlesborough and Newcastle.

Estimated levels of ascertainment

Table 6 shows capture-recapture estimated levels of case ascertainment. Even with the figures for men and women combined, the confidence intervals on the estimated

number of amputations tended to be broad. For minor amputations in Leicester and Ilan the numbers were either too small, or the overlaps between the data sources inadequate, to enable meaningful capture-recapture estimates to be made. For first amputations, estimates of ascertainment were low (less than 70 per cent) in two centres, Tochigi and Vicenza. In three (Leeds, Middlesborough and Montgomery county) they were above

Table 6 Estimated (using capture-recapture methods) total number of first and all major and minor amputations and estimated ascertainment of amputations in each centre for men and women combined

Centre		First amputations				All amputations			
		No. identified from overlapping sources	Estimated no.	Total no identified	Estimated ascertainment (%)	No. identified from overlapping sources	Estimated no	Total no identified	Estimated ascertainment (%)
Leeds, UK	Major	175	189 (181–202)	185	97.9	213	226 (216–241)	226	100
	Minor	172	178 (173–183)	190	93.7	233	241 (236–248)	269	100
Leicester, UK	Major	82	102 (89–207)	89	87.3	108	153 (119–297)	108	70.6
	Minor	—*	—*	37	—*	—*	—*	48	—*
Madrid, Spain	Major	12	19 (16–25)	20	100	21	25 (21–37)	25	100
	Minor	18	23 (19–38)	18	78.3	24	32 (25–56)	24	75.0
Middlesbrough, UK	Major	74	81 (75–94)	74	91.4	99	101 (99–104)	103	100
	Minor	51	53 (52–56)	55	100	69	71 (69–74)	73	100
Montgomery, USA	Major	256	256 (255–258)	256	100	403	403 (402–403)	403	100
	Minor	174	174 (173–175)	174	100	257	257 (256–258)	257	100
Navajo area, USA	Major	61	69 (62–91)	62	89.9	80	93 (83–110)	83	66.9
	Minor	92	128 (106–193)	93	72.7	145	184 (159–243)	149	81.0
Newcastle, UK	Major	69	78 (71–89)	69	88.5	86	118 (93–212)	86	72.9
	Minor	35	39	36	92.3	54	59 (55–69)	55	93.2
Ilan, Taiwan	Major	55	57 (55–60)	55	96.5	66	68 (66–73)	66	97.1
	Minor	—*	—*	11	—*	—*	—*	13	—*
Tochigi, Japan	Major	103	156 (128–209)	105	67.3	—	—	—	—
	Minor	16	30 (17–381)	16	53.3	—	—	—	—
Vicenza, Italy	Major	37	71 (46–161)	43	60.6	54	76 (61–108)	56	73.7
	Minor	24	63 (33–214)	23	36.5	30	78 (44–214)	34	43.6

Values in parentheses are 95 per cent confidence intervals. *In these centres there was insufficient overlap between the different sources to use capture-recapture. In some centres the numbers identified from overlapping sources were different (in all cases by no more than 5 per cent) from the numbers in Tables 2–5. This is for two reasons. First, a few amputations were identified from non-overlapping sources and, second, for two patients in Newcastle age could not be determined from the data available and so they were not included in the age-specific rates

90 per cent for first major and minor amputations. All the rest fell somewhere between 72 per cent and 95 per cent. The interpretation and value of these estimates is addressed in the Discussion.

Age and sex distribution of patients having an amputation

Although the overall rates varied greatly between centres, the age and sex distribution of amputations were very similar. Thus in all centres the incidence of both major and minor amputations in both men and women rose steeply with age; the largest increases came between the age groups of 40–59 and 60–79 years (Tables 2–5). Around two-thirds of amputations occurred in patients aged over 60 years, with the exception of minor amputations in men and women in the Navajo area. Overall amputation rates were substantially higher in men than in women, from 17 per cent higher crude rates for first major amputations in Leicester, to 400 per cent higher for all major and minor amputations in Madrid. The exceptions to this were first and all major amputations in Vicenza, where crude rates were higher in women than men (entirely accounted for by high rates in

women aged 80 years and over), and for first minor amputations in Leeds where the rates in men and women were similar.

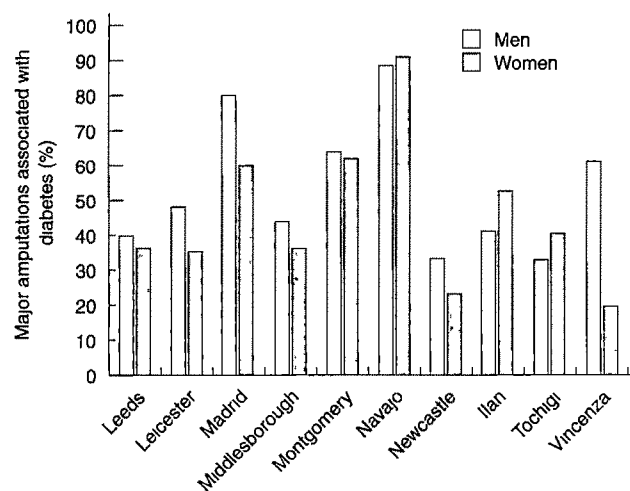
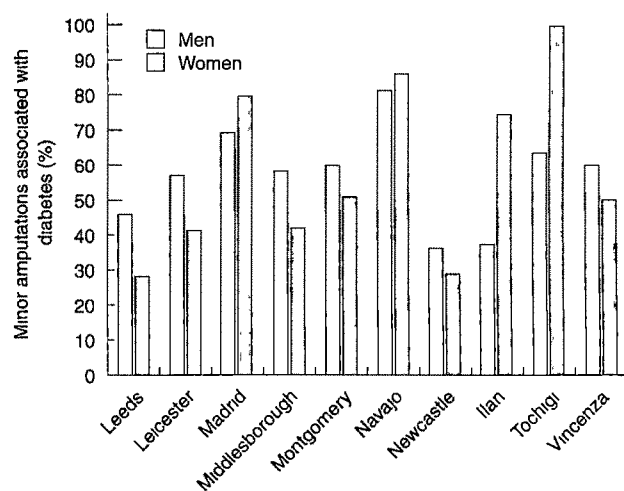
Relationship of major to minor, and all to first amputations

In most centres the incidence of both first and all major amputations was greater than the incidence of first and all minor amputations, respectively (Table 2–5). The most extreme exception to this was the Navajo area where the crude incidence of major amputations was between 50 per cent (all, men) and 79 per cent (first, women) of the incidence of minor amputations. As would be expected, the incidence of all amputations was greater than the incidence of first amputations in almost all centres. The only exception was for minor amputations in Ilan where the rates were similar. In the other centres, rates of all amputations were higher than rates of first amputations from 10 per cent (major amputations in men in Ilan) up to 251 per cent (major amputations in women in Montgomery county). Most were 20–40 per cent higher.

Table 7 Conditions associated with first ever major and minor amputations

		Men				Women			
		Trauma	Diabetes	Infection	PVD	Trauma	Diabetes	Infection	PVD
Leeds, UK	Major	4	40	57	83	10	36	58	70
	Minor	10	46	60	57	0	29	33	26
Leicester, UK	Major	0	48	33	88	2	36	17	81
	Minor	5	57	43	62	0	41	12	59
Madrid, Spain	Major	0	80	60	93	0	60	40	100
	Minor	8	69	77	100	0	80	80	80
Middlesbrough, UK	Major	10	44	54	77	9	36	50	73
	Minor	0	59	71	65	5	43	38	62
Montgomery, USA	Major	3	64	14	72	2	62	9	60
	Minor	2	60	32	89	1	51	26	68
Navajo area, USA	Major	10	90	85	51	0	91	100	65
	Minor	6	81	88	16	10	86	90	17
Newcastle, UK	Major	10	33	37	71	15	23	31	62
	Minor	14	36	54	64	0	29	29	50
Ilan, Taiwan	Major	50	41	53	56	16	53	84	74
	Minor	57	38	43	43	25	75	75	75
Tochigi, Japan	Major	3	33	49	55	0	41	22	30
	Minor	0	64	27	36	20	100	40	20
Vicenza, Italy	Major	0	61	22	78	4	20	4	88
	Minor	7	60	60	60	12	50	38	62

Values are percentages. More than one condition may be present per patient. PVD, peripheral vascular disease.

**Fig. 3** Percentage of first ever major amputations associated with diabetes**Fig. 4** Percentage of first ever minor amputations associated with diabetes

Conditions associated with amputations

Table 7 shows the percentage of first major and minor amputations associated with trauma, diabetes, infection and peripheral vascular disease for men and women in each of the centres. More than one condition was often present per patient. The proportion of amputations associated with diabetes varied from between 20 and 30 per cent (major amputations in women in Vicenza and

major and minor amputations in women in Newcastle) up to 80 per cent and above, such as in men and women in the Navajo area (Figs 3 and 4). These figures provided no information on the incidence of amputation in people with diabetes. In general there was a strong positive relationship between the percentage of amputations associated with diabetes and the percentage associated with infection. Obvious exceptions to this were major amputations in men in Montgomery county, and major

and minor amputations in men and major amputations in women in Tochigi, Japan.

In nine of the ten centres the percentage of major amputations associated with trauma in men was 10 per cent or less. The exception to this was Ilan in Taiwan where 50 per cent of major amputations were associated with trauma. The highest percentages of major amputations associated with trauma in women were in Newcastle (15 per cent) and Ilan (16 per cent). The percentage of major amputations associated with peripheral vascular disease in men ranged from 51 per cent in the Navajo area to 93 per cent in Madrid. The percentages were similar in women, with the exception of Tochigi where only 30 per cent were associated with peripheral vascular disease.

Discussion

This paper presents data on lower extremity amputation from ten centres in six countries. There were some striking contrasts between the centres. There were marked differences between centres in the incidence of amputations, in the proportion associated with diabetes and in the ratio of first to all amputations. Equally noteworthy were the similarities between the centres in the distribution of amputations by age and sex, despite differences in overall rates. The methodology used in this study was designed, within the limits of routine data sources, to provide valid comparisons between the centres. Amputation case definitions and presentation of rates were identical for each centre. Greater scepticism exists with regard to whether the level of ascertainment of amputations between centres was comparable and the comparability of some specific data items from medical records.

In order to maximize ascertainment and to allow checks on ascertainment level, each centre used more than one data source. Estimates of ascertainment using capture-recapture methods suggested that there were indeed some differences in levels of ascertainment. Capture-recapture estimates of ascertainment were used as an aid to interpretation of the results rather than providing robust estimates of the 'true' rates. The wide confidence intervals of many of the estimates in *Table 6* illustrate the uncertainty around the point estimates and indeed the known difficulty in modelling this type of data⁵. In addition, where only two data sources were available these tended to be positively dependent, meaning that the capture-recapture estimate will overestimate the level of ascertainment⁶. None the less the use of this technique provided useful information. Thus, the capture-recapture estimates suggested that in two of the centres with the lowest rates, Tochigi and Vicenza, there may have been substantial underascertainment, in the order of 50 per cent. However, even doubling the amputation

rates of these centres, they remained substantially below those in the north of England and North America. There remained large differences in amputation rates between the centres even when allowing for potential differences in ascertainment; the lowest rates were in Spain, Japan and Taiwan and the highest in the Navajo area. Within western Europe, and to a lesser extent England, there were also marked differences in amputation rates between some of the centres.

The high levels of lower extremity amputation in native American populations are well described⁸ and are associated with a high prevalence of diabetes^{9,10}. The low incidence of amputation in the centres in Japan, Taiwan, Spain and Italy contrasts with the higher rates in the north of England and Montgomery, USA. Recent data suggest that the prevalence of diabetes in Spain, Italy, Japan and Taiwan is at least twice as high as in England and similar to that in the USA¹¹. Clearly a higher prevalence of diabetes is unlikely to be the main explanation for these differences in incidence of amputation. Differences in the prevalence of peripheral vascular disease may be more relevant, although data are scarce. For example, in the Edinburgh Artery Study the prevalence of peripheral vascular disease was 30 per cent in men and women aged 55–74 years¹². In a study of elderly Italian men and women¹³ the prevalence was 10 per cent, and in a Japanese study of village residents aged 60–79 years a prevalence of 0.6 per cent was reported¹⁴. The World Health Organisation international study of people with diabetes aged 35–54 years found a huge variation in the prevalence of lower limb vascular disease, with the lowest prevalence in Tokyo and Hong Kong¹⁵. The relatively low incidence of amputation in Leicester compared with the other English centres fits with previous findings from Leicester¹⁶, in both its general and Indo-Asian populations. Within England, data on the epidemiology of peripheral vascular disease are also scarce but there is evidence for a south to north gradient¹⁷ and for differences by ethnic group¹⁸.

This study also evaluated the conditions associated with, or potential causes of, amputation. These data were abstracted from medical records and are acknowledged to be prone to omissions and inaccuracies¹⁹. The highest proportion of amputations associated with trauma was in Ilan, Taiwan, where some 57 per cent of minor amputations reportedly followed injury. Excluding patients who had amputations associated with trauma, as is often done in the presentation of amputation rates, made little difference to the ranking of the centres. The proportion of amputations associated with diabetes ranged from 20 per cent (major amputations in women in Vicenza) to over 90 per cent. For major amputations in men the lowest proportion associated with peripheral vascular disease was

51 per cent in the Navajo, and in women was 30 per cent in Tochigi. The proportion associated with peripheral vascular disease tended to be lower for minor amputations; the converse was true for the proportion associated with infection.

In conclusion, there were marked differences in the incidence of amputations between ten centres in six different countries, but with similar distributions by age and sex. Rates were highest in the North American and northern European centres and lowest in Spain, Taiwan and Japan. In one population (Navajo) a very high prevalence of diabetes was likely to be the explanation for the high amputation rates. Differences between the other populations did not seem to be related to the prevalence of diabetes; it seems likely that differences in the prevalence of peripheral vascular disease are important. Other factors, such as cultural and medical care differences²⁰, including access to vascular surgery services, may also be important, but require further investigation.

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Prospective study of the effect of laparoscopic hemifundoplication on motor and sensory function of the proximal stomach

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Background: Some 30 per cent of patients develop dyspeptic symptoms following antireflux surgery. These symptoms may result from alterations in the motor and sensory function of the proximal stomach.

Methods: Proximal gastric motor and sensory function was studied with an electronic barostat in 12 patients with reflux who underwent laparoscopic hemifundoplication. In addition, 24-h pHmetry, gastric emptying (scintigraphy) and vagus nerve integrity (pancreatic polypeptide response to hypoglycaemia) were assessed. Fifteen healthy volunteers served as controls.

Results: Laparoscopic hemifundoplication significantly decreased total acid exposure time ($P < 0.05$). Vagus nerve function remained intact in all but one patient. The mean(s.e.m.) lag phase for emptying of solids was significantly shorter after operation than before (15(3) versus 21(3) min; $P < 0.05$). Proximal gastric compliance was not significantly different before and after fundoplication. However, mean(s.e.m.) postprandial relaxation was significantly reduced ($P < 0.05$) after hemifundoplication compared with the value before operation (3341(1105) versus 12763(3616) ml over 90 min) and in controls (14567(2358) ml over 90 min). Postprandial fullness was significantly increased after hemifundoplication ($P < 0.05$). Postprandial gastric relaxation correlated with the lag phase for emptying of solids ($r = 0.55$, $P < 0.02$).

Conclusion: After hemifundoplication, proximal gastric compliance is not altered but postprandial relaxation is impaired and associated with sensations of fullness and shorter duration of the lag phase for emptying of solids.

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Introduction

Surgical treatment for gastro-oesophageal reflux disease (GORD) is indicated in patients who are refractory to optimal medical therapy or in need of lifetime medical treatment. In well selected cases, and when performed by experienced surgeons, the success rate in controlling reflux can be as high as 90 per cent^{1,2}. Different mechanisms of action of fundoplication have been proposed. Fundoplication may increase the resting pressure at the lower oesophageal sphincter (LOS) and reduce the frequency of transient LOS relaxation^{3,4}, both of which are important factors in the pathogenesis of reflux.

Despite effective control of reflux, up to 30 per cent of patients undergoing antireflux surgery develop new symp-

toms such as fullness, early satiety, abdominal pain, dysphagia, bloating and occasionally also diarrhoea^{5,6}. Although the underlying mechanisms are poorly understood, most of these symptoms have been attributed to anatomical and functional alterations of the gastro-oesophageal region induced by the fundoplication^{7–9} or to vagus nerve injury^{10,11}. The present study was designed to evaluate prospectively the effect of laparoscopic hemifundoplication on motor and sensory function of the proximal stomach in the fasting state and after meal ingestion (postprandial relaxation) using an electronic barostat. In addition, the effect of antireflux surgery on 24-h pHmetry, gastric emptying and vagus nerve integrity was also measured and related to the barostat findings. Data were compared with those obtained from healthy controls.

Patients and methods

Twelve patients (six men and six women) of mean(s.e.m.) age 43(4) (range 32–65) years with therapy-resistant GORD who were considered candidates for antireflux surgery were included in the study. Before operation all patients underwent upper gastrointestinal endoscopy, 24-h ambulatory oesophageal pH monitoring, vagus nerve function testing and a gastric emptying test. GORD was diagnosed by a typical clinical history, oesophagitis detected at endoscopy and/or abnormal oesophageal acid exposure as measured by ambulatory 24-h pH monitoring¹². All patients underwent laparoscopic hemifundoplication. To evaluate the outcome of fundoplication, 24-h pHmetry, vagus nerve function testing and the gastric emptying test were repeated 6 months after surgery. The barostat study was also performed before and 6 months after hemifundoplication.

Fifteen healthy subjects (four men and 11 women) of mean(s.e.m.) age 34(4) (range 22–56) years served as controls. None had gastrointestinal disease or had previously undergone abdominal surgery.

The protocol was approved by the ethics committee of Leiden University Medical Centre.

Gastric barostat

An electronic barostat (Synectics Visceral Stimulator; Synectics Medical, Stockholm, Sweden) was used to distend the stomach^{13,14}. A polyethylene bag (maximum capacity 950 ml) was tied to the end of a multilumen tube (19 Fr). This catheter was connected to the barostat. The barostat measures gastric motor activity as changes in intragastric volume at a constant intragastric pressure, and vice versa^{13,14}.

Study protocol

All experiments were started at 08.00 hours after an overnight fast of at least 10 h. All medication interfering with the measurements was stopped at least 4 days before the experiment. The catheter with bag was introduced through the mouth into the fundus. The correct position was checked by means of fluoroscopy^{15,16}. Subjects were seated in a comfortable lying chair in a semirecumbent position with the lower extremities just above abdominal level.

Perception of the sensations of fullness and nausea was quantified during the experiment using a 100-mm visual analogue scale. A 200-ml liquid meal (Nutridrink; Nutricia, Zoetermeer, The Netherlands) containing 10 g protein, 36 g carbohydrate and 13 g fat was used as a test meal (300 kcal).

The following procedures were performed:

- 1 Isobaric distension: increase in pressure in steps of 1 mmHg every 90 s from 0 to 14 mmHg or when a maximum bag volume of 750 ml was reached. The intragastric bag was then deflated within 3 min. Minimal distending pressure (MDP) was determined.
- 2 Recovery period of 30 min.
- 3 Barostat procedure: the barostat was set at a pressure of MDP + 2 mmHg. After 15 min recording under fasting conditions, the test meal was ingested (time zero) and the measurement was continued for 90 min.

Gastric emptying

Gastric emptying of solids and liquids was measured with a dual-isotope method. The solid component of the meal consisted of a pancake (280 kcal) labelled with 15 MBq technetium-99m colloid and the liquid component was 150 ml water labelled with 2 MBq indium-111 diethylenetriamine penta-acetate¹⁷. Anterior images of gastric activity were taken for 120 min starting from the onset of meal with a frequency of one image per minute. Data were analysed to determine the lag phase, half-emptying time and emptying rate for the solid component. The retention for liquids was calculated at 15, 30, 60 and 90 min after meal ingestion.

Vagus nerve integrity

Vagus nerve integrity was measured indirectly by the response of plasma pancreatic polypeptide to insulin-induced hypoglycaemia as described previously^{18,19}. Pancreatic polypeptide concentration was measured by a sensitive and specific radioimmunoassay²⁰. The nadir of blood glucose in response to insulin was below 2.5 mmol/l in all patients. A peak increment in plasma pancreatic polypeptide concentration below 47 pmol/l is considered to be compatible with truncal vagotomy¹⁸.

Data analysis

Proximal gastric compliance was considered as the slope of the pressure–volume curve starting at the level of MDP, and was determined by calculating the coefficient of linear regression. Intragastric bag volumes before and after the meal, measured during the barostat procedure, were calculated as the mean intragastric bag volume over 5-min periods. Postprandial intragastric bag volumes were also calculated as the integrated incremental area under the relaxation curve (AUC) after subtraction of the fasting volume at time zero (meal ingestion). Perception scores were calculated relative to baseline values. Phasic volume

waves were defined as changes in intragastric bag volume of more than 30 ml that reverted in less than 2 min to a volume within 50 per cent of the previous level^{13,21}. The frequency of these volume waves was calculated for 15-min intervals during the barostat procedure.

Statistical analysis

Results of gastric emptying, vagus nerve function testing and 24-h pHmetry were analysed with the Wilcoxon signed rank test. Linear regression analysis was used to calculate correlations between gastric emptying and barostat parameters. MDP, basal and postprandial gastric volumes were analysed for statistical significance by repeated analysis of variance. When this indicated a probability of less than 0.05 for the null hypothesis, Student–Newman–Keuls analyses were performed to determine which values between or within groups differed significantly. The significance level was set at $P < 0.05$.

Results

Vagus nerve integrity

Before operation all patients had a plasma pancreatic polypeptide peak increment in the normal range (greater than 47 pmol/l), with a mean (s.e.m.) value of 140 (11) pmol/l. After the fundoplication, plasma pancreatic polypeptide concentration was normal in all but one patient, who had a peak value compatible with 'truncal vagotomy'. This patient was not included in further analysis but relevant data are presented separately in *Table 1*. The mean (s.e.m.) value of postoperative peak plasma pancreatic polypeptide increment of the other 11 patients was 124 (22) pmol/l.

Preoperative and postoperative symptoms and 24-h pHmetry

Before operation all patients had symptoms of reflux. Hemifundoplication completely resolved symptoms of heartburn and regurgitation in ten of 12 patients. Two patients still complained of heartburn and their total acid exposure time did not improve significantly after operation; one of them was the patient with vagus nerve dysfunction. Mean acid exposure time of the 11 patients without vagus nerve dysfunction is shown in *Table 2*.

Barostat measurement

Isobaric distension. Mean (s.e.m.) preoperative MDP was not significantly different from postoperative MDP (5.7 (0.4) versus 6.2 (0.5) mmHg) and was similar to that in

Table 1 Details of the barostat investigation and gastric emptying tests for the patient with evidence of vagus nerve dysfunction after hemifundoplication

	Before operation	After operation
Barostat measurement		
Proximal gastric compliance (ml/mmHg)	61	71
Basal gastric tone (ml)	231	295
Maximal postprandial volume (ml)	420	446
AUC (ml over 90 min)	18 954	10 162
Gastric emptying test		
Solids		
Lag phase (min)	10	22
Half emptying time (min)	111	157
Emptying rate (% per h)	29	22
Liquid retention (%)		
15 min	40	47
30 min	26	25
60 min	19	20
90 min	14	15

AUC, area under the relaxation curve

Table 2 Results of 24-h pHmetry and gastric emptying tests before and after hemifundoplication in 11 patients with gastro-oesophageal reflux disease without postoperative vagus nerve dysfunction

	Before operation	After operation
Percentage time at pH < 4*		
Total	8.7 (3.5–18.4)	3.9 (0.4–14.4)‡
Upright	8.7 (2.3–19.8)	3.8 (0.8–22.4)‡
Supine	6.4 (4.8–17.2)	0.05 (0–10.4)‡
Gastric emptying test†		
Solids		
Lag phase (min)	21(3)	15(3)‡
Half emptying time (min)	95(7)	84(7)
Emptying rate (% per h)	40(2)	44(2)
Liquid retention (%)		
15 min	47(5)	55(5)
30 min	30(3)	36(6)
60 min	15(2)	19(3)
90 min	8(2)	9(2)

Values are *median (range) and †mean (s.e.m.). ‡ $P < 0.05$ (Wilcoxon signed rank test)

controls (5.7 (0.4) mmHg). There was a linear relationship between intragastric pressure and volume during pressure distension ($P < 0.001$). Proximal gastric compliance, measured as the slope of the pressure–volume curve starting at the level of MDP, was not significantly different before and after fundoplication (55.5 (6.3) versus 59.6 (5.0) ml/mmHg) and in controls (50.1 (6.1) ml/mmHg).

Postprandial gastric relaxation. The mean(s.e.m.) basal intragastric bag volume at MDP + 2 mmHg was similar before and after fundoplication (178(21) *versus* 183(26) ml) and was not significantly different from that in controls (140(10) ml). After meal ingestion, bag volume increased significantly ($P < 0.01$) and reached its maximal volume 15 min postprandially (Fig. 1). The mean(s.e.m.) maximal postprandial intragastric bag volume was significantly lower ($P < 0.05$) after fundoplication compared with the value before operation (264(36) *versus* 416(34) ml) and in controls (409(25) ml). Postprandial intragastric bag volume returned significantly faster to basal level in patients after fundoplication than it did before operation (30(3) *versus* 90(8) min; $P < 0.05$). The AUC during the total postprandial period after fundoplication (3341(1105) ml over 90 min) was significantly smaller ($P < 0.05$) than that before fundoplication (3341(1105) *versus* 12 763(3616) ml over 90 min) and in controls (14 567(2358) ml over 90 min).

Perception. During pressure distension the sensation of fullness increased to the same extent in all groups (Fig. 2a). The sensation of fullness at 15 min after meal ingestion was significantly more pronounced postfundoplication compared with prefundoplication and control values ($P < 0.05$) (Fig. 2b). No alterations in nausea or discomfort were observed after hemifundoplication.

Volume waves. Mean(s.e.m.) fasting volume wave frequency was not significantly different before and after hemifundoplication (1.2(0.1) *versus* 1.0(0.2) per min) compared with controls (1.3(0.1) per min). The degree of postprandial changes in volume wave frequency was similar before and after operation and in controls.

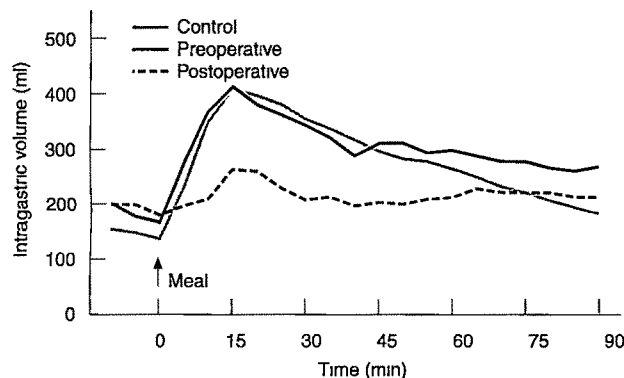


Fig. 1 Mean intragastric volume before and after operation during the application of minimal distending pressure + 2 mmHg before and after ingestion of a 200-ml liquid meal in 11 patients without vagus nerve dysfunction and in 15 healthy controls

Gastric emptying

Results of gastric emptying for solids and liquids before and after hemifundoplication are shown in Table 2. There was a significant positive correlation between the lag phase and

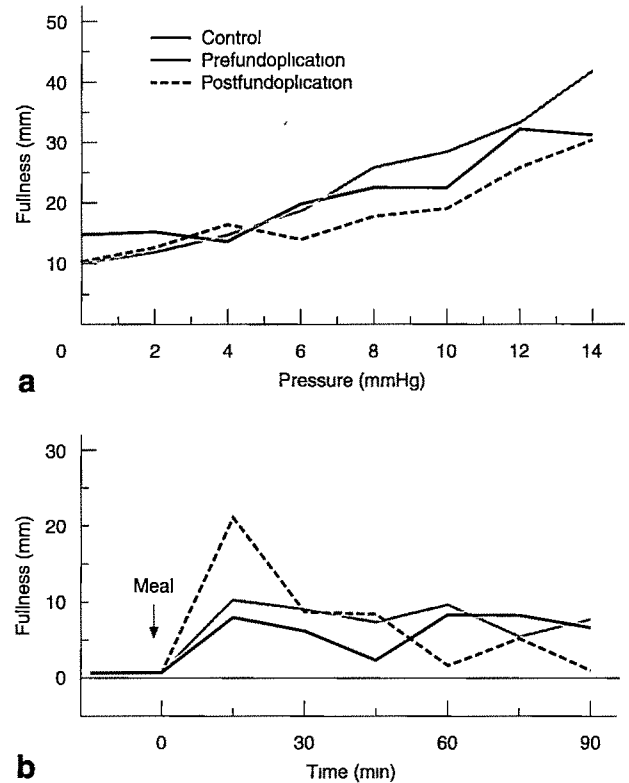


Fig. 2 Sensation of fullness (determined on a 100-mm visual analogue scale) before and after operation in 11 patients without vagus nerve dysfunction and in 15 healthy controls. **a** During isobaric distension; **b** in response to a 200-ml liquid meal

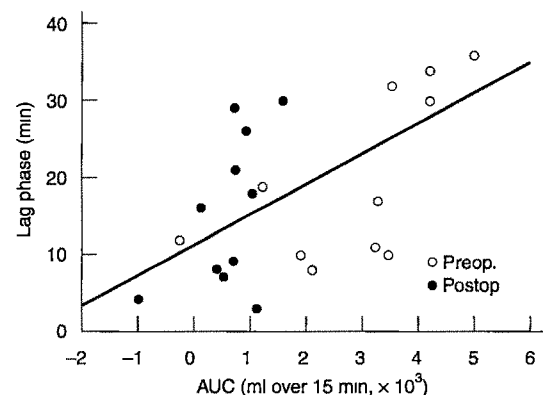


Fig. 3 Correlation between the lag phase of emptying for solids and the area under the relaxation curve (AUC) during the first 15 min postprandially in 11 patients without vagus nerve dysfunction before and after operation. $r = 0.55$, $P < 0.02$

AUC during the first 15 min postprandially ($r=0.55$, $P<0.02$) (Fig. 3). Half emptying time for solids was also significantly correlated with total postprandial intragastric bag volume ($r=0.47$, $P<0.05$).

Vagus nerve dysfunction

Data relating to the patient with evidence of vagus nerve dysfunction are shown in Table 1. It is important to note that the results of this patient are not in line with those of the 11 patients with intact vagus nerve function.

Discussion

Previous studies have shown that partial fundoplication is associated with a lower incidence of postoperative dysphagia and gas bloat syndrome compared with Nissen fundoplication, while both techniques are equally effective in controlling reflux^{22,23}. It has been documented that the type of fundoplication performed correlates significantly with postoperative dysphagia and oesophageal manometric findings²⁴. Proximal gastric motor and sensory function have previously been shown to be impaired after laparoscopic Nissen fundoplication compared with findings in a group of reflux controls¹⁶. The present study is the first to evaluate prospectively the effect of laparoscopic hemifundoplication on the motor and sensory function of the proximal stomach using an electronic barostat. Although the study population was small ($n=12$), patients were evaluated in detail. Because of the high prevalence of postoperative dysphagia (10–30 per cent) seen after total fundoplication, the present authors prefer hemifundoplication. The 12 patients reported in this study were enrolled between July 1997 and February 1998 and underwent, in addition to the standard preoperative and postoperative evaluation, gastric emptying and barostat studies.

The results reveal that proximal gastric compliance is not affected after hemifundoplication. Postprandial gastric relaxation, on the other hand, is significantly reduced while abdominal symptoms are significantly increased after hemifundoplication.

In line with previous results^{16,25,26}, the present study revealed that proximal gastric compliance was not significantly different from that in controls either before or after operation. As gastric compliance reflects the viscoelastic property of the gastric wall, this finding indicates that neither reflux disease nor hemifundoplication affects this feature of the proximal stomach. Furthermore, MDP and basal volume were similar in the three groups, indicating that fasting proximal gastric motor function remains intact in reflux disease and after hemifundoplication. Consistently, no differences in the sensation of fullness

and nausea were observed during pressure distension and basal barostat measurement before or after hemifundoplication.

After meal ingestion, the degree and duration of postprandial proximal gastric relaxation were significantly reduced after hemifundoplication. Several mechanisms may be involved: (1) alterations in the proximal gastric wall, (2) vagus nerve injury or (3) reduced fundal capacity. The first possibility can be excluded since proximal gastric compliance, tone and volume waves that reflect the characteristics of the proximal gastric wall were similar before and after operation. Results of the vagus nerve function test eliminate the possibility of a damaged vagus nerve as the cause of impaired postprandial gastric relaxation. Thus, loss of fundal capacity due to hemifundoplication remains the most likely mechanism underlying the postprandial abnormalities found after operation.

In parallel with the smaller postprandial volume increment, an increased sensation of fullness was observed after hemifundoplication. Impaired fundic relaxation with increased distribution of food to the distal stomach has been reported in dyspeptic patients with postprandial bloating and early satiety^{27,28}.

Delayed gastric emptying has frequently been observed in association with GORD^{29,30}. Nissen fundoplication enhances gastric emptying^{31,32}. In the present study, the lag phase of gastric emptying for solids was significantly shorter after hemifundoplication. As shown in Fig. 3, the early phase of postprandial proximal gastric relaxation correlated significantly with the duration of the lag phase. Although not statistically different before and after operation (probably due to type 2 error), half emptying time for solids was none the less significantly related to total postprandial gastric relaxation. These observations support the role of postprandial gastric relaxation in the process of food emptying from the stomach. Utilizing a part of the fundus reduces postprandial gastric volume (higher gastric tone) and may accelerate the transfer of chyme to the distal part of the stomach³³.

In summary, this prospective study has shown that proximal gastric compliance is not affected after hemifundoplication. Hemifundoplication results in impaired postprandial proximal gastric relaxation, which is probably responsible for the increased sensation of fullness after meal ingestion and shorter duration of the lag phase of gastric emptying for solids.

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Diagnostic accuracy of needle-localized open breast biopsy for impalpable breast disease

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Background: Needle-localized open breast biopsy (NLBB) is considered the gold standard procedure for the diagnosis of impalpable breast disease. In an observational follow-up study the sensitivity and negative predictive value of this procedure was determined in a clinical population with long-term follow-up.

Methods: Some 199 consecutive patients with a benign histological diagnosis on NLBB were followed for the occurrence of breast cancer, using information from the Dutch National Morbid-Anatomical Record Department. Based on a review of mammograms and histological slides, an expert panel decided whether the carcinomas detected during follow-up were newly developed, or were present already at the time of the NLBB.

Results: After a median follow-up of 60.5 months, seven carcinomas were detected. At panel review, six appeared to have been missed by NLBB. The sensitivity of NLBB was 99 per cent after 2 years of follow-up, but dropped to 96 per cent after 5 years. Similarly, the negative predictive value dropped from 99 per cent after 2 years to 94 per cent after 5 years of follow-up.

Conclusion: NLBB is an accurate diagnostic procedure for the evaluation of impalpable breast disease. However, with longer follow-up the accuracy becomes lower than generally reported.

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Introduction

The advent of nationwide breast cancer screening programmes and the subsequent increase in screening mammography has led to a significantly higher detection rate of impalpable breast lesions¹. Needle-localized open breast biopsy (NLBB) is considered the gold standard procedure for the diagnosis of impalpable breast disease^{2,3}. The number of screening-induced NLBBs in the Netherlands has risen from 556 in 1990 to 3502 in 1996¹. In addition, a large number of impalpable breast lesions have been detected outside the screening project.

Although NLBB is a proven procedure with a low complication rate^{4,5}, it requires an operation under general anaesthesia, and many patients and physicians consider it traumatic. In the Netherlands, approximately 40 per cent of patients undergoing NLBB have benign breast disease¹. Newer, less invasive techniques such as ultrasonography or

stereotactically guided large-core needle biopsy have recently been advocated as alternatives to obtain a histological diagnosis^{6–8}.

Analysis of the diagnostic accuracy of new techniques is based on comparison with the previous gold standard⁹. Several studies have addressed the diagnostic accuracy of NLBB for impalpable lesions, showing accuracy rates of 96.6–100 per cent^{10–14}. However, the long-term sensitivity and negative predictive value of NLBB is not known. The present study evaluated the diagnostic accuracy of NLBB for impalpable breast disease in a clinical population with long-term follow-up.

Patients and methods

By means of the hospital registry, all patients who had NLBB between January 1987 and October 1995 in the University Medical Center Utrecht were identified. The

open biopsy technique involved insertion of a hooked wire under mammographic or ultrasonographic guidance to localize the lesion. Subsequently, a breast specimen encompassing the tip of the needle was removed surgically. To confirm the presence of the suspicious lesion, a specimen radiograph was performed. Finally, the biopsy specimen was examined histologically and further treatment was planned if necessary.

The histological diagnoses of the open biopsy specimens were divided into five categories: (1) normal breast tissue, (2) benign breast disease, (3) atypical hyperplasia (ductal or lobular) or lobular carcinoma *in situ*, (4) ductal carcinoma *in situ* (DCIS) and (5) invasive carcinoma. Patients with DCIS or invasive cancer were treated accordingly. Lesions in categories 1–3 required no further treatment and were therefore considered benign. These patients were included in a historical cohort and followed for the development of breast cancer.

Two follow-up procedures were applied to obtain maximum information regarding the development of breast cancer in these patients. First, all nationwide pathology reports up to October 1998 were provided by the Dutch National Morbid-Anatomical Record Department (PALGA). PALGA is a national database in which nationwide reports of cytological and histological examinations are registered. Since 1990, every national pathology laboratory has been connected to PALGA. Because of possible incomplete PALGA data between 1987 and 1989, patient files were linked to those of the Comprehensive Cancer Centre Middle Netherlands. Accordingly, patients with breast cancer diagnosed in hospitals in the surroundings of the University Medical Center Utrecht were identified. Second, the patients' general practitioners were contacted; medical records were examined for information about the development of breast cancer and to verify any patients lost to follow-up.

A panel, comprising a radiologist (R.M.P.), a surgeon (I.H.M.B.R.) and a pathologist (M.E.I.S.), reviewed mammograms, medical records and histological slides of patients diagnosed with breast cancer during follow-up. Based on lateralization, localization, size and appearance of the lesion, and correctness of the open biopsy procedure, the panel established whether the cancers found during follow-up were already present at the time of the initial open biopsy procedure. If so, the open biopsy procedure was classified as 'false negative'.

Sensitivities and negative predictive values were calculated at various follow-up intervals (after 2, 3, 4 and 5 years). Data were administered and analysed using the Statistical Package for Social Sciences 7.5 (SPSS, Chicago, Illinois, USA). Exact confidence intervals were calculated.

Results

Between January 1987 and October 1995, 346 patients underwent NLBB for 353 impalpable lesions. The clinical characteristics of these patients and the results of the radiological and histological examinations of the lesions are presented in Table 1. Two hundred lesions in 199 patients were classified as benign. These patients had complete follow-up for a median interval of 60.5 (range 1–141) months; 191 patients (96 per cent) were followed for at least 2 years, 180 (90 per cent) for at least 3 years, 137 (69 per cent) for a minimum of 4 years and 100 lesions (50 per cent) were followed for more than 5 years. Of the 19 patients with less than 3 years' follow-up, six had died within 3 years of the open biopsy procedure, two as a result of disseminated breast cancer from the contralateral breast and four from unrelated causes. For six patients no medical record/general practitioner follow-up information was available and seven patients had less than 3 years' follow-up (range 1–33 months).

During follow-up, 15 patients had a second ipsilateral surgical procedure. Eight benign lesions were found but seven breast carcinomas were diagnosed. At panel review it appeared that one of these carcinomas was newly developed. This carcinoma was detected 31 months after the NLBB procedure. The panel concluded that the six other carcinomas had already been present at the time of the initial NLBB (three invasive ductal carcinomas, two

Table 1 Characteristics of 346 patients and 353 impalpable breast lesions included in the study

Mean (range) age (years)	55 (29–81)
Screen-detected lesions	171 (48)
Family history of breast cancer	52 (15)
History of breast cancer	32 (9)
Mammographic features	
Microcalcification	161 (46)
Mass with microcalcification	39 (11)
Mass	104 (29)
Spiculated mass	43 (12)
Focal asymmetry	1 (0)
Architectural distortion	1 (0)
Missing	4 (1)
Histology of open biopsy specimen	
Normal breast tissue	4 (1)
Benign	190 (54)
Fibroadenoma	33 (17)*
Fibrocystic disease	115 (61)*
Other benign disease	42 (22)*
Atypical ductal hyperplasia/ lobular carcinoma <i>in situ</i>	6 (2)
Ductal carcinoma <i>in situ</i>	44 (12)
Invasive carcinoma	109 (31)

Values in parentheses are percentages unless otherwise indicated,

*percentage of benign tumours

Table 2 Impact of follow-up on sensitivity and negative predictive value of needle-localized open breast biopsy with initial benign biopsy in 199 patients

	Follow-up (years)			
	2	3	4	5
No at risk	191	180	137	100
False-negative biopsy	2	3	5	6
Sensitivity (%)	99 (95–100)	98 (95–100)	97 (93–99)	96 (92–99)
Negative predictive value (%)	99 (96–100)	98 (95–100)	96 (92–100)	94 (87–98)

Values in parentheses are 95 per cent confidence intervals

invasive ductal carcinomas with an extensive intraductal component and one invasive lobular carcinoma with an extensive intraductal component).

The reason for missing the carcinoma was erroneous placement of the needle guidewire in four patients. The tip of the needle was situated more than 2 cm away from the lesion in each case. In one patient, the surgeon wrongly assumed the lesion to be localized in the lateral upper quadrant instead of the lateral lower quadrant and therefore the incorrect area was excised. Finally, in one patient the pathologist failed to diagnose an invasive lobular carcinoma. The six missed carcinomas were detected after 20, 21, 29, 45, 45 and 60 months. All patients, except one, underwent follow-up mammography after 6–12 months. Nevertheless, the missed tumours were not recognized at that time (although they were evident, in retrospect).

The sensitivity and negative predictive value of NLBB for the diagnosis of impalpable breast lesions is presented in Table 2. The sensitivity was 99 (95 per cent confidence interval 95–100) per cent after 2 years of follow-up and 96 (92–99) per cent after 5 years. The negative predictive value for a benign diagnosis on open breast biopsy was 99 (96–100) per cent after 2 years of follow-up and 94 (87–98) per cent after 5 years.

Discussion

In this study, NLBB had a sensitivity of 99 per cent and a negative predictive value of 99 per cent for the diagnosis of impalpable breast cancer after follow-up of 2 years. However, after 5 years the sensitivity and negative predictive value dropped to 96 and 94 per cent respectively. These results demonstrate that long-term follow-up is important for estimating the diagnostic performance of NLBB; three of the six missed cancers were detected more than 3 years after NLBB, although follow-up mammography had been performed.

To determine whether this study population was representative of the general situation in the Netherlands, the incidence of breast cancer in this cohort was computed.

Two new primary breast carcinomas (one ipsilateral and one contralateral) developed in 199 women (age range 29–81 years) during a total of 1056 person-years of follow-up. Although the rate (1.89 per 1000 person-years) is based on only two cases and is therefore not reliable, it is comparable to the incidence in the Netherlands for women with the same weighted age distribution (1.96 per 1000 person-years)¹⁵.

The results of the present study compare unfavourably with those in the literature and general belief. It is, however, difficult to compare results between researchers because follow-up intervals and procedures vary among studies. The diagnostic accuracy of NLBB has been the subject of various publications. In a study by Bender *et al.*¹⁰, of 412 patients with a benign open biopsy, no cancers were missed but long-term follow-up was not the aim of the study and the median follow-up was not reported. Jackman and Marzoni¹² reported seven missed lesions (2.5 per cent) from 280 impalpable lesions, including one carcinoma. However, missed lesions were defined as inconsistencies between histology and mammography or absence of the lesion on specimen radiography. Also, long-term follow-up was not the aim of their study. Similarly, other studies addressing the diagnostic accuracy of NLBB did not have long-term follow-up^{11,14}.

Factors leading to failure of NLBB can be divided into three categories: localization, surgical and histological. Accurate needle placement is important for successful removal of the lesion; four of the six carcinomas in the present series were missed because of inappropriate needle placement. Jackman and Marzoni¹² reported that if the lesion was penetrated by the localization needle, it was always successfully removed. Accurate needle placement can be difficult when mammography only is available. More precise needle placement can be achieved using more advanced localization techniques such as stereotaxis and ultrasonography. Peeters *et al.*¹³ reviewed false-negative open biopsy results in screen-detected lesions; besides imprecise needle placement owing to difficult localization of the lesion, reasons for missed cancers included failure to

diagnose malignancy at histological examination and the fact that specimen radiography was not performed routinely.

Specimen radiography is considered to be of great importance in reducing the number of missed lesions¹⁶. In the present study a specimen radiograph was performed in almost all patients, including five of the six patients with a false-negative biopsy result. In four, the specimen radiograph was incorrectly considered to contain the lesion. This is in accordance with the findings of Hasselgren *et al.*¹⁷ who reported a false-positive rate of 1.8 per cent for specimen radiography.

Recognition of missed lesions is most likely to be achieved by multidisciplinary team assessment of original mammograms, localization films, specimen radiography, the surgeon's account of any difficulties at biopsy and the resulting histology. Where there is a discrepancy between mammography and histology or any doubt over the correctness of the procedure, mammography performed 6–12 weeks after the open biopsy procedure might reduce the rate of missed lesions.

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Intraperitoneal polypropylene mesh repair of incisional hernia is not associated with enterocutaneous fistula

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Background: Incisional hernia repair with prosthetic material is followed by fewer recurrences than primary repair. Polypropylene is the most commonly used prosthetic material but may cause enterocutaneous fistulas. The aim of this study was to determine whether enterocutaneous fistulas developed after incisional hernia repair with polypropylene mesh and to evaluate clinical outcome after incisional hernia repair.

Methods: A retrospective analysis of the outcome of incisional hernia repair with polypropylene mesh between 1982 and 1998 was conducted. Follow-up data were obtained from medical records and questionnaires.

Results: Polypropylene incisional hernia repair was performed in 136 patients. Median follow-up was 34 months. No enterocutaneous fistulas developed. Wound infection occurred in 6 per cent. Wound sinus formation occurred in two patients. No mesh was removed because of infection and no persisting infection of the mesh occurred.

Conclusion: Enterocutaneous fistula formation appears to be very rare after incisional hernia repair with polypropylene mesh, regardless of intraperitoneal placement, omental coverage or closing of the peritoneum.

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Introduction

Incisional hernias develop in 2–19 per cent of patients after abdominal surgery^{1–5}. After primary repair, until recently the method of choice, recurrence occurs in up to 46 per cent^{6–10}. Tension-free repair with prosthetic material lowered the reported recurrence rate to between 2.2 and 10 per cent^{1,11} but is not recommended when contact between the mesh and bowel is unavoidable. Plastic prostheses were first used in 1958¹² and proved to be easy to use, pliable, and showed no disintegration with ageing. Polypropylene mesh has become the most widely used prosthetic material for repair of incisional hernias^{13,14}. This mesh is available in a monofilament (Marlex; Davol, Cranston, Rhode Island, USA) and a double-filament (Prolene; Ethicon, Somerville, New Jersey, USA) form.

An early report by Usher *et al.*¹² suggested that placing the mesh in direct contact with omentum or bowel could be done safely. However, enterocutaneous fistula was first described in 1981 as a late complication of intraperitoneal

placement of a polypropylene mesh in a patient¹⁵. After reports of other enterocutaneous fistulas following mesh repair of incisional hernias, this technique was no longer recommended^{13,16,17}. However, enterocutaneous fistula formation was not mentioned by Molloy *et al.*¹⁴, Liakakos *et al.*¹⁸ and Sugerman *et al.*¹⁹ as a long-term complication after incisional hernia repair with mesh. Therefore, it remains unclear what the potential danger is of intraperitoneal non-resorbable mesh used without omental or peritoneal coverage of the bowel. Series of incisional hernia repairs with polypropylene mesh have been described by other authors^{13,14,18–20}, but the possible association between intraperitoneal placement of polypropylene mesh and fistula formation has not been discussed extensively.

The aim of this retrospective study was to determine whether or not enterocutaneous fistulas occurred after repair of incisional hernias with polypropylene mesh, and to assess whether it can be considered safe to perform intraperitoneal polypropylene mesh repair with or without coverage of bowel with omentum or peritoneum.

Patients and methods

Patients undergoing incisional hernia repair with the use of mesh between September 1982 and August 1998 were identified by the Department of Medical Registration. The medical records of these patients were examined and data regarding incisional hernia repair with mesh were entered into a database (SPSS-data entry; SPSS, Chicago, Illinois, USA).

A mild wound infection was defined as redness surrounding the laparotomy wound, a moderate infection produced pus and a severe infection was defined as wound dehiscence and wound edge necrosis. Wound sinus was defined as a non-healing defect of the wound extending into the subcutaneous tissue.

Statistical analysis of possible recurrence-related factors was performed with Kaplan–Meier curves and comparisons between curves were made by the log rank test. Other comparisons were made according to the Pearson χ^2 test.

Follow-up data were acquired either from the medical records if patients had been visiting the outpatient clinic or from a questionnaire sent to the patient's general practitioner. This questionnaire contained questions about whether the patient had visited the general practitioner since the incisional hernia repair and if this visit was related to the hernia repair.

A Medline search on incisional hernia repair with cross-references identified other series of incisional hernia repair. The results of these series were summarized and compared with the present results.

Results

Incisional hernia repair with the use of prosthetic material was performed in 171 patients between 1 September 1982 and 1 August 1998. A polypropylene mesh was inserted in 136 patients (80 per cent) and a polytetrafluoroethylene patch (Gore-Tex; W. L. Gore, Phoenix, Arizona, USA) in 16; in 13 patients a Vicryl mesh (Ethicon) was added to a polypropylene mesh and in six only Vicryl was used to close the defect. Only the patients who had solely polypropylene meshes were included in this analysis ($n = 136$). This group consisted of 69 men and 67 women of mean(s.d.) age 62(12) years. Laparotomy had been performed in the midline in 71 per cent of these 136 patients, was oblique (appendicectomy and cholecystectomy) in 18 per cent and transverse in 11 per cent. An upper midline incision was the most common location of incisional hernias (38 per cent). Some 72 per cent of incisional hernias were primary, 16 per cent were recurrent, 7 per cent had recurred for the second time and 5 per cent had recurred more than twice. The median(s.d.) diameter of the fascial defect was 6(5) cm.

At induction of anaesthesia for surgical repair of the incisional hernia, 82 per cent of all patients received antibiotic prophylaxis. Only 4 per cent of all incisional hernia repairs with polypropylene were performed as an emergency operation for incarceration. A serosal lesion of the bowel occurred in 7 patients (5 per cent) and bowel perforation occurred in three (2 per cent) at operation. Major perioperative bleeding did not occur in any patient. In most patients (84 per cent), the mesh was placed subfascially. The omentum was placed between mesh and bowel in 27 patients (20 per cent) and in 39 patients (29 per cent) the peritoneum could remain closed or was closed during the repair. In 57 patients (42 per cent) it was not possible to place omentum between the mesh and bowel or to close the peritoneum. In 13 patients (10 per cent) the surgical report was inconclusive about interposition of peritoneum or omentum. The mesh was fixed with non-resorbable sutures in 90 per cent. In six patients the surgical procedures were performed under contaminated conditions, because of accidental bowel perforation ($n = 3$), planned bowel resection ($n = 2$) or restoration of continuity after ileostomy ($n = 1$). No patient was operated on for a burst abdomen. Prophylactic antibiotics were administered in 82 per cent of all repairs. Every patient with contamination during incisional hernia repair received antibiotics perioperatively.

In 49 per cent of surgical procedures a drain was left behind, which was removed after a median(s.d.) time of 2(1) days. Antibiotic prophylaxis was administered perioperatively in all patients with drains. The median(s.d.) operative time was 100(42) min and duration of stay in hospital was 7(7) days.

Six patients (4 per cent) were lost to follow-up. Recurrence of incisional hernia occurred in 19 patients (3-year recurrence rate 18 per cent), after a median(s.d.) follow-up of 10(38) months. *Table 1* shows the results of analysis of factors possibly related to the development of recurrence. Patients without recurrence ($n = 111$) had a median(s.d.) duration of follow-up of 34(30) months.

No enterocutaneous fistulas were encountered during follow-up. Early postoperative complications consisted of wound infection (two mild, one moderate and five severe), haematoma ($n = 2$), ileus ($n = 2$) and bleeding from the surgical wound ($n = 3$). In two patients reoperation was necessary, the first because of a bowel perforation not identified during initial surgery and the second because of loosening of the inserted mesh resulting in wound dehiscence. Removal of the mesh was not necessary in these patients. In two patients a wound sinus developed in the operative field, both of whom underwent emergency repair with a suprafascially placed mesh and received antibiotic prophylaxis. Both sinuses were treated conservatively. Six seromas (4 per cent) were reported, all of which were treated

Table 1 Overview of patient-related factors related to recurrence rate

	3-year recurrence (%)	P*
Age		
≤ 70 versus > 70 years	12 versus 33	0.01
Antibiotics		
Yes versus no	0 versus 18	0.02
Size of hernia		
≤ 6 versus > 6 cm	13 versus 25	0.12
Primary versus recurrent hernia	15 versus 24	0.21
Placement		
Subfascial versus suprafascial	20 versus 12	0.46
Sutures		
Resorbable versus non-resorbable	25 versus 18	0.54
Wound infection		
Yes versus no	19 versus 0	0.17
Total	18	

*Log rank test comparing Kaplan-Meier curves

conservatively. In four of these cases the mesh was placed subfascially and in two suprafascially; a drain was placed in three of the patients.

Discussion

An overview of other series of incisional hernia repair is given in Table 2. In 567 patients only three enterocutaneous fistulas were reported (0.5 per cent).

A number of authors^{13,15-17,20} have described enterocutaneous fistula formation after incisional hernia repair. Kaufman *et al.*¹⁵ described a single patient with a burst abdomen due to wound infection and necrosis of the abdominal wall after operation. The defect in the abdom-

inal wall was closed with the use of polypropylene during an emergency operation. Afterwards an enterocutaneous fistula developed. Miller and Junger¹⁶ described the development of a fistula after laparoscopic repair of an inguinal hernia that recurred for the seventh time. An enterocutaneous fistula developed although the peritoneum was closed after positioning the mesh. According to the authors, close contact between the mesh and bowel resulted in low-grade infection of the mesh whereafter the mesh eroded through the visceral peritoneum into the ileum, causing a local infection and consequently an ileocutaneous fistula.

Seelig *et al.*¹⁷ described one patient who suffered from a burst abdomen that was closed successively with a Vicryl mesh, a polypropylene mesh and another polypropylene mesh because of incisional hernia recurrence. After 9 months an enterocutaneous fistula developed. Leber *et al.*¹³ observed two enterocutaneous fistulas in a group of 135 patients who underwent incisional hernia repair with polypropylene mesh. No specific details about these patients were reported but it was suggested that the development of enterocutaneous fistula was correlated with previous wound infection. White *et al.*²⁰ reported one enterocutaneous fistula after mesh repair but no details were described.

In the present study, no fistula occurred in a group of 136 patients. The results show that enterocutaneous fistula formation need not to be feared in elective incisional hernia repair with polypropylene mesh. In 42 per cent of incisional hernia repairs the polypropylene mesh was placed intraperitoneally without coverage of the bowel by omentum or peritoneum. In 49 per cent of repairs the omentum was placed between the mesh and bowel, or the peritoneum was

Table 2 Overview of published series of incisional hernia repair

	Leber <i>et al.</i> ¹³	Molloy <i>et al.</i> ¹⁴	Liakakos <i>et al.</i> ¹⁸	Sugerman <i>et al.</i> ¹⁹	White <i>et al.</i> ^{20*}	Vrijland <i>et al.</i>
No. of patients	135	50	49	98	99	136
Mean hernia diameter (cm)	9.8	n.a.	n.a.	173†	9.9	6.0‡
Antibiotics	n.a.	50 (100)	49 (100)	98 (100)	90 (91)	112 (82)
Subcutaneous drain	n.a.	50 (100)	'Almost all'	98 (100)	56 (57)	67 (49)
Position of mesh	Various	Suprafascial	Onlay	Suprafascial	Onlay (50) Inlay (28) Other (22)	Subfascial 114 (84) Suprafascial 22 (16)
Non-resorbable sutures	n.a.	Yes	Yes	Yes	n.a.	(90)
Wound infection	7 (5)	4 (8)	2 (4)	17 (17)	16 (16)	8 (6)
Seroma formation	n = n.a. (<3)	2 (4)	n.a.	n.a.	21 (21)	6 (4)
Enterocutaneous fistula	2 (1)	0	0	0	1 (1)	0
Recurrence	n = n.a. (17)	4 (8)	4 (8)	4 (4)	n.a.	(18)
Wound sinus	n.a.	6 (12)	2 (4)	n.a.	n.a.	2 (1)
Mean follow-up	6.7 years	45 months	7.6 years	20 months	1-144 months	34 months‡

Values in parentheses are percentages. *Not solely polypropylene repair. †Mean surface area (cm²); ‡median. n.a., Data not available

or remained closed. The goal of these procedures is to prevent fistula formation. Leber *et al.*¹³ suggested a beneficial effect of these procedures whereas Molloy *et al.*¹⁴ and Larson and Harrower²¹ placed the mesh intraperitoneally without omental or peritoneal coverage of the intestines. Both described no complications.

The use of prosthetic materials for incisional hernia repair has significantly lowered the reported recurrence rates; the 3-year recurrence rate was 18 per cent in this series. This percentage is higher than that reported by others^{1,11,14,18,19}.

Advanced age predisposed to a higher recurrence rate after incisional hernia repair. Impaired wound healing in older patients^{22,23} is a probable cause of the significant difference in recurrence between patients over 70 years of age and younger patients.

Whether prophylactic antibiotics are necessary has been subject to discussion. The wound infection rate after incisional hernia repair with prosthetic material was 6 per cent ($n = 8$) and removal of the mesh was not necessary in any patient. Houck *et al.*²⁴ described an infection rate of 15 per cent and White *et al.*²⁰ reported wound infections in 14 per cent although prophylactic antibiotics were administered almost routinely. No correlation could be shown between placement of drains and infection rate in the present study. Two patients suffered from wound sinuses which were both treated conservatively. Molloy *et al.*¹⁴ described a wound sinus formation rate of 12 per cent, of which two-thirds needed surgical intervention.

A significant difference in recurrence was found between patients who received antibiotics and those who did not, and therefore prophylactic antibiotics should be used in every incisional hernia repair. No relation was found between subfascial insertion of the mesh or insertion of a drain and the development of seroma. To minimize seroma formation Larson and Harrower²¹ advised subfascial placement of the prosthetic mesh. Most authors prefer suprafascial placement of the mesh to prevent long-term complications^{13,14,19,20}, but this may predispose to seroma formation. However, the present results suggested no relation between insertion of a subcutaneous drain and a decrease in seroma formation.

In conclusion, polypropylene mesh can be placed safely intraperitoneally but this should be performed under antibiotic cover.

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Postoperative outcome and sites of recurrence in patients following curative resection of gastric cancer

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Background: Recurrence occurs in a variety of forms and in different organs after 'curative resection' of gastric cancer. This study investigated the postoperative prognosis for each type of recurrence.

Methods: From 1969 to 1988, 939 patients with gastric cancer underwent curative resection; data on 130 of 207 patients who died with recurrence were analysed. Attention was focused on the site of recurrence and the postoperative outcome.

Results: Haematogenous recurrence was evident in 54 per cent (70 of 130 patients), peritoneal recurrence in 43 per cent (56 of 130), lymph node recurrence in 12 per cent (16 of 130) and local recurrence in 22 per cent (29 of 130). Thirty-three patients (25 per cent) had recurrences at multiple sites. Peritoneal and local recurrences were related to infiltrative growth, in contrast to haematogenous and lymphatic recurrences. There were no statistical differences in survival time among each type of recurrence and survival was not related to the number of sites of recurrence. Survival did not depend on factors of sex, age, tumour location, tumour size, depth of invasion, tissue differentiation, histological growth pattern, lymphatic and vascular involvement, lymph node metastasis and extent of lymph node dissection.

Conclusion: The clinicopathological characteristics of gastric cancer determine the type of recurrence, although the clinical outcome is the same for each type of tumour and is not related to the number of sites of recurrence.

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Introduction

Early tumour detection, standardized surgical treatment, including lymph node dissection, and appropriate adjuvant therapy have improved the survival of patients with gastric cancer¹. The recurrences are in a variety of forms and are related to the level of tumour invasion^{2–4}. Rates of cancer-related death are lower for patients with early gastric cancer⁵, but recurrences in these cases are associated with blood-borne metastases from well differentiated tumours. In patients with advanced gastric cancer, peritoneal recurrence is more frequent, and in patients with poorly differentiated tumours recurrence occurs earlier than in those with lower grade tumours⁶. These issues present valuable information for designing postoperative treatment protocols.

In this study, the clinicopathological characteristics and outcome of patients with recurrence were reviewed following surgical resection of potentially curable gastric cancer. Particular emphasis was placed on the sites and distribution

of recurrences and on the relationship with the original tumour stage and postoperative prognosis.

Patients and methods

Between 1969 and 1988, 939 patients with gastric cancer underwent potentially curative resection. Gastric resection was standardized and the resection margin was as follows: early tumours (defined as a lesion in the mucosa, or mucosa and submucosa⁵), 2 cm for localized tumour and 4 cm for infiltrative tumour; advanced tumours (defined as tumour penetrating the muscularis propria), 3 cm for localized tumour and 6 cm for infiltrative tumour. Complete excision of adjacent locally invaded organs was performed in the absence of peritoneal dissemination, liver metastasis or widespread nodal involvement⁷. Lymph node dissection was classified as follows: D₁, complete removal of group 1 lymph nodes alone; D₂, complete removal of group 1 and 2 lymph nodes; D₃, complete removal of group 1, 2 and 3 lymph nodes. Lymph node dissection was at the D₂ or D₃

level for approximately 90 per cent of patients. Remaining patients underwent D₁ dissection, because of more advanced age, organ dysfunction and/or general clinical condition. All patients were staged clinically and pathologically. Pathological staging and classification of the resected gastric cancer were made according to the general rules for gastric cancer study in surgery and pathology in Japan⁸. Lymph node metastases in group 1, 2 and 3 nodes are referred to as n1, n2 and n3 respectively.

After operation, patients were entered into a regular follow-up program which entailed a combination of blood examinations, radiological examination of the gastrointestinal tract, endoscopic procedures, computed tomography and ultrasonography. Follow-up was every 3 months for the first year and then at intervals of 6–12 months for at least 5 years.

Of the 939 patients, 207 died from gastric cancer-related causes, 49 from another cancer, 137 with another disease and 17 from undetermined causes. Of the 207 gastric cancer-related deaths, the sites of recurrence were determined precisely for 130 patients by radiography, computed tomography and/or ultrasonography, and these patients are the focus of this report. In 77 other patients, the cause of death was obtained from the local physician and was often, but not always, confirmed by checking the death certificate.

Statistical analysis

The BMDP Statistical Package program (BMDP, Los Angeles, California, USA) for the IBM 3090 mainframe computer (Armonk, New York, USA) was used for all analyses⁹. The BMDP 4F and 3S programs were used for the χ^2 and Kruskal–Wallis tests to compare data on the groups. The BMDP 1L program was used to analyse survival time by the Kaplan–Meier method, and the Mantel–Cox test was used to test for differences between survival curves. The BMDP LR program was used for simultaneous multivariate adjustment of each covariate, using a backward stepwise logistic regression analysis¹⁰. In this analysis, age and tumour size were included as continuous variables. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological factors

Table 1 shows clinicopathological data on the 130 patients who underwent gastric resection and who died following recurrence; they are grouped according to the type of recurrence. There was a haematogenous recurrence in 70

Table 1 Analysis of recurrences for each site of recurrence

Recurrence	No. of sites			
	1	2	3	4
Haematogenous (<i>n</i> = 70)	43	22	3	2
Peritoneal (<i>n</i> = 56)	33	17	4	2
Lymphatic (<i>n</i> = 16)	4	6	4	2
Local (<i>n</i> = 29)	17	9	1	2
Details of 130 cases	97	27	4	2

patients (54 per cent), a peritoneal recurrence in 56 (43 per cent), lymph node recurrence in 16 (12 per cent) and a local recurrence in 29 (22 per cent). Haematogenous recurrence occurred in the liver in 43 patients, in the lung in 16, in bone in four and in the brain in seven. Thirty-three patients (25 per cent) had recurrence at multiple sites, making a total of 74 sites of recurrence. Each clinicopathological factor was analysed statistically among the four groups of recurrence type (Table 2). Peritoneal and local recurrences occurred more frequently in patients whose tumour had an infiltrative growth pattern. There were no differences in other clinicopathological factors, including sex and age, among each site of recurrence.

Survival rates

At the time of data analysis, the median length of follow-up was 24.3 (range 1.6–119.2) months. Survival data for these patients, who died from gastric cancer, were compared for each site of recurrence (haematogenous, peritoneal, lymphatic and local recurrence), and for single or multiple sites of recurrence (Table 3). The cancer-related postoperative outcome was the same for each site of recurrence, and was irrespective of the number of sites of recurrence.

Postoperative survival time was also determined in relation to each clinicopathological factor (Table 4). There were no differences in survival time according to the presence or absence of recurrence, tumour size, depth of invasion, tissue differentiation, histological growth pattern, lymphatic invasion, vascular invasion, lymph node metastasis, and extent of lymph node dissection. There were also no differences between men and women, younger and older patients, and location of the tumour.

Discussion

The metastatic potential of gastric cancer has been correlated with the expression level of several independent genes that regulate cell growth¹¹. Like other neoplasms,

Table 2 Clinicopathological characteristics of patients with each form of recurrence

	Haematogenous (n=70)	Peritoneal (n=56)	Lymphatic (n=16)	Local (n=29)
Mean(s.d.) maximal tumour diameter(cm)	7.3(4.0)	8.2(3.5)	6.5(2.5)	8.1(3.5)
Depth of invasion				
m, sm	9	3	1	2
mp, ss, se, si	61	53	15	27
Tissue differentiation				
Well	32	17	6	11
Poor	38	39	10	18
Histological growth pattern*				
Non-infiltrative	40	15	8	11
Infiltrative	29	40	8	18
Unknown	1	1		
Lymphatic invasion				
Negative	24	18	3	10
Positive	46	38	13	19
Vascular invasion				
Negative	44	43	9	22
Positive	25	12	7	6
Unknown	1	1		1
Lymph node metastases				
Negative	15	13	2	4
Positive	54	43	14	25
Unknown	1			
Lymph node dissection				
D ₁	10	5	1	5
D ₂ and D ₃	60	51	15	24

m, Mucosa, sm, submucosa; mp, muscularis propria, ss, subserosa, se, serosa, si, infiltrating adjacent organs. * $P=0.006$ (peritoneal and local *versus* haematogenous and lymphatic recurrences, Pearson's χ^2 test)

Table 3 Survival rates at 1, 3 and 5 years for patients who died with recurrence of gastric cancer, as related to each site of recurrence and the number of recurrence sites

Recurrence	n	Survival rate (%)		
		1 year	3 years	5 years
Haematogenous	70	81	27	7
Peritoneal	56	75	27	11
Lymphatic	16	94	31	19
Local	29	72	38	14
Single	97	77	30	5
Multiple	33	80	26	14

human gastric cancers are heterogeneous and consist of multiple subpopulations of cells with different metastatic potentials. Patterns of haematogenous, peritoneal, lymph node and local recurrences are closely related to the biological behaviour of cancer cells³; however, there have been few reports on clinical outcome for each type of recurrence.

Haematogenous metastases have been noted in advanced cases, but also in patients with early gastric cancer². Haematogenous recurrence was thought to occur mainly

when cancer cells released from the primary site entered the vascular system and were transported to the organ, where attachment and proliferation occurred¹². The main locus of vascular invasion was most frequently in the submucosal layer, which is richly endowed with lymph and blood capillaries¹³; thus liver metastasis could occur even in the early stages of gastric cancer, particularly in patients with evident vascular invasion¹⁴. The present authors have previously reported on the possible role of vascular and lymphatic spread of gastric cancer to distant organs in patients with advanced disease, and that vascular invasion and lymph node metastasis were independent risk factors for synchronous and metachronous liver metastasis¹⁵. Poorly differentiated tissue with infiltrative growth was noted mainly in patients with an advanced level of invasion into the serosal layer or adjacent organs³. Peritoneal recurrence occurred particularly in advanced gastric cancer of the poorly differentiated tissue type, and was associated with serosal invasion and lymph node metastasis. In these cases, the tumour cells infiltrate the gastric wall and penetrate the serosa. Poorly differentiated cancer cells are thought to disseminate trans-serosally to the peritoneum. Moreover, in cases with an advanced level of invasion, lymphatic and/or vascular routes account for spread of the

Table 4 Survival time for patients who died with recurrence of gastric cancer, as related to each clinicopathological factor

	n	Survival rate (%)		
		1 year	3 years	5 years
Maximal tumour diameter (cm)				
≤ 6.8*	65	86	34	9
> 6.8	65	69	25	6
Depth of invasion				
m, sm	11	77	45	9
mp, ss, se, si	119	77	27	7
Tissue differentiation				
Well	51	82	29	7
Poor	79	74	27	7
Histological growth pattern				
Non-infiltrative	58	81	28	9
Infiltrative	72	74	29	7
Lymphatic invasion				
Negative	39	85	33	10
Positive	91	75	28	7
Vascular invasion				
Negative	86	78	28	9
Positive	44	78	32	5
Lymph node metastasis				
Negative	27	74	37	11
Positive	103	79	28	7
Lymph node dissection				
D ₁	14	71	29	7
D ₂ and D ₃	116	78	29	8

*6.8 cm is the median level of tumour size m, Mucosa; sm, submucosa; mp, muscularis propria, ss, subserosa, se, serosa, si, infiltrating adjacent organs

cancer cells to the peritoneum and distant organs¹⁵. Local recurrence was noted in 22 per cent of patients with a recurrence after curative resection, even though the resection line was determined to be sufficiently distant from the macroscopic edge of the tumour. As lymphatic and vascular vessels are abundant in the gastric wall, tumour extension by these routes may be related to local recurrence of the tumour¹³. Although recurrences other than lymphatic recurrence occurred in a single site in 60 per cent of patients for each type of recurrence, lymphatic recurrence occurred in combination with other types of recurrence in 75 per cent of cases. Thus, the type of recurrence varied with characteristics of the gastric cancer, and the incidence increased in proportion to the depth of invasion⁴.

The rate of recurrence has been reported to be lower in patients with early invasion, where the tumour is confined to the mucosal and submucosal layers^{16,17}. When death from gastric cancer only was included in the survival analysis of all patients, the postoperative prognosis was better for those with early gastric cancer⁵. However, the postoperative outcome in patients with early gastric cancer and who died

with a recurrence was as poor as that for patients with an advanced stage of primary tumour. In addition, there were no differences in survival time, related to the number or sites of recurrence. Therefore, the metastatic potential of gastric cancer is closely related to the postoperative outcome. Patients at risk for cancer-related death after potentially curative operation should be managed to try to prevent tumour recurrence. The authors reported on the role of proliferating cell nuclear antigen or p53 abnormality in the metastatic potential of gastric cancer^{3,18}. In an attempt to improve early detection of recurrence, biological characterization is needed to develop follow-up protocols for regular computed tomography and/or tumour marker determination.

The present findings show that the clinicopathological characteristics of gastric cancer determine the type of recurrence, although the clinical outcome is the same for each type and is not related to the number of sites of recurrence.

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Changing patterns in the management of gastric volvulus over 14 years

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Background: Gastric volvulus is an uncommon condition, which can be difficult to diagnose and treat. This study represents a large series of patients with the condition.

Methods: All patients presenting with gastric volvulus over a 14-year period were reviewed.

Results: Some 36 patients (median age 75 years) were identified. Volvulus, usually secondary to a hiatus hernia, presented acutely in 29 patients. The major symptoms were abdominal pain, vomiting and upper gastrointestinal haemorrhage. The most useful investigations were barium contrast studies and upper gastrointestinal endoscopy, which were helpful in 21 of 25 and 11 of 18 patients respectively. Treatment was conservative in five patients, by open surgery in 13 and laparoscopic repair in 18 (three converted to open operation). There were no major complications and no deaths. Median hospital stay was shorter in patients treated by laparoscopic rather than open surgery (6 (range 4–36) *versus* 14 (7–50) days; $P < 0.05$).

Conclusion: Acute and chronic gastric volvulus can be treated successfully by either open or laparoscopic surgery. However, laparoscopic surgery now represents a safe and acceptable approach, with minimal morbidity and a significantly shorter hospital stay. This is likely to be of considerable benefit for the treatment of a predominantly elderly population, often with significant co-morbidity.

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Introduction

Gastric volvulus is an uncommon condition, comprising abnormal rotation of the stomach along its longitudinal (organoaxial) or transverse (mesenteroaxial) axis. When the rotation exceeds 180°, gastric obstruction or strangulation may occur. In 30 per cent of patients, the volvulus occurs as a primary event¹, but it is more commonly secondary to other causes, such as paraoesophageal hiatus hernia, traumatic diaphragmatic hernia, eventration of the diaphragm, abdominal bands or adhesions¹. Gastric volvulus occurs predominantly in older adults, although it has been described in children and adolescents. Mortality rates of 30–50 per cent have been reported for acute volvulus, the major cause of death being strangulation, leading to necrosis, perforation and hypovolaemic shock^{1,2}.

The classical presentation of acute gastric volvulus is a triad of severe epigastric pain, vomiting followed by retching without the ability to vomit, and difficulty or inability to pass a nasogastric tube³. The additional features of chronic gastric volvulus include dysphagia, vomiting, waterbrash, gastro-oesophageal reflux and breathlessness⁴.

Treatment of acute gastric volvulus is either conservative or surgical, the latter traditionally requiring a laparotomy

for reduction of the volvulus and correction of underlying causes, with or without fixation of the stomach by gastropexy⁴. More recent approaches include gastropexy alone, either at laparotomy⁵ or by percutaneous endoscopic gastrostomy (PEG)^{6–10}, and laparoscopic techniques^{11,12}. As well as facilitating gastrostomy placement, endoscopy has been used for the reduction of acute gastric volvulus^{13,14}. Combinations of endoscopic, open or laparoscopic approaches have also been reported^{11,15–17}.

Previous reports of gastric volvulus are limited, the largest review describing 27 patients⁴, and before 1993 there were no reports of laparoscopic repair¹. Since then several papers have addressed laparoscopic management, primarily of chronic gastric volvulus¹¹, but all have been anecdotal descriptions of isolated patients. This study addresses recent trends in management, in particular the evolution of laparoscopic treatment.

Patients and methods

This study entailed a retrospective analysis of all patients with gastric volvulus who presented to the Professorial Surgical Unit at the Royal Adelaide Hospital between July

1985 and June 1999 inclusive. Patients were identified by computer analysis of hospital discharge records. Following detailed case note review, data collection was facilitated by use of a standard pro forma. The specific issues addressed included patient demographic details, incidence, aetiology, presentation, investigation and treatment. No patient was excluded from the series.

Statistical analysis was by Mann-Whitney *U* test for the comparison of non-parametric data sets, using SPSS for Windows version 6.0 (SPSS, Chicago, Illinois, USA). $P < 0.05$ was regarded as statistically significant.

Results

Thirty-six patients (13 men and 23 women) with gastric volvulus were identified. The median age was 75 (range 25–92) years. Twenty-six patients were aged over 65 years and 18 over 75 years. The mean incidence in this population was 2.6 new patients per million per year.

Volvulus was primary in three and secondary in 31 patients. In two patients the information was insufficient for classification. The most common predisposing factor was a paraoesophageal hiatus hernia (28 patients). Three cases were iatrogenic; one followed PEG insertion and two followed laparoscopic Nissen fundoplication early in this institution's experience with the procedure¹⁸. Of ten patients in whom the anatomical classification was recorded, nine had organoaxial and one mesenteroaxial volvulus. The presentation was acute in 29 patients and chronic in seven. The presenting features are given in Table 1.

The most common investigations were barium study (25), plain chest radiography (19), endoscopy (18) and plain abdominal radiography (eight). Four patients underwent oesophageal manometry and pH studies, two were investigated by computed tomography, one by colonoscopy and

one by abdominal ultrasonography. The diagnostic yield is shown in Table 2.

Of the 29 acute presentations, three patients were managed conservatively, 13 by open surgery and 13 laparoscopically, of which two procedures were converted to open operation. Of the seven patients with chronic volvulus, two were treated conservatively and five laparoscopically, with one conversion to open operation. Operation entailed reduction of the volvulus, repair of any associated hiatal hernia and a loose Nissen fundoplication when appropriate. All patients who underwent laparoscopic operation had preliminary nasogastric tube decompression of the obstructed stomach. All patients who underwent operation had a concurrent fundoplication, except two in the laparoscopic group in whom there were technical difficulties in performing the wrap.

There were no major complications and no postoperative deaths. Three patients who had a laparoscopic procedure complained of postoperative dysphagia, which settled spontaneously in all, and none required reoperation. All complications, except one case of dysphagia and one of cardiac dysrhythmia, occurred in patients with acute volvulus. None of the patients treated conservatively re-presented with problems.

The overall median hospital stay was 10 (range 0–50) days. The median stay was 8 (range 0–24) days for patients treated conservatively, 14 (range 7–50) days for the open surgery group and 6 (range 4–36) days for the laparoscopic group ($P < 0.05$, laparoscopic *versus* open groups).

Discussion

Treatment of gastric volvulus has changed in recent decades. Thirty years ago, Tanner outlined the methods of surgical repair⁴. These included diaphragmatic hernia repair, division of bands, simple gastropexy, gastropexy with division of the gastrocolic omentum (Tanner's

Table 1 Presenting features of acute and chronic gastric volvulus

Presenting symptom	Acute	Chronic	Total
Abdominal pain	24	6	30
Vomiting	17	3	20
Upper GI bleed/anaemia	9	2	11
Abdominal distension	5	0	5
Gastro-oesophageal reflux	5	2	7
Dysphagia	4	3	7
Respiratory symptoms/chest pain	7	0	7
Postprandial discomfort	3	0	3
Altered bowel habit	2	0	2
Excess flatulence	2	0	2
Acute confusion	1	0	1
Dehydration	1	0	1

GI, gastrointestinal

Table 2 Investigations ordered and diagnostic yield

Investigation	Ordered	Diagnostic	Suggestive	No yield
Barium study	25	14	7	4
Chest radiography	19	0	5	14
Upper GI endoscopy	18	5	6	7
Abdominal radiography	8	0	3	5
Manometry/pH	4	0	0	4
Chest computed tomography	2	0	1	1
Colonoscopy	1	0	0	1
Abdominal ultrasonography	1	0	0	1

GI, gastrointestinal

operation), partial gastrectomy, gastrojejunostomy, fundoantral gastrogastrostomy (Opolzer's operation) and repair of eventration of the diaphragm. Open surgical reduction, with or without gastropexy, has been the traditional treatment, although in view of the magnitude of the surgical insult in a predominantly elderly population, a conservative management policy has often been pursued, particularly for chronic volvulus. However, in recent years less invasive techniques, such as PEG placement and laparoscopic surgery, have become available. The authors believe that surgical repair is superior to PEG placement, as the latter alone may not prevent recurrent volvulus.

The diagnosis of gastric volvulus can be difficult. In this series, the most common investigations were barium contrast studies, endoscopy, and plain chest and abdominal radiography. Barium studies provided the greatest yield, being diagnostic in 14 of 25 patients and suggestive of volvulus in seven. Endoscopy was diagnostic in five of 18 patients and suggestive in six. A plain abdominal radiograph was never diagnostic and was suggestive in only three of eight patients. Plain chest radiographs were not diagnostic but were suggestive in five of 19 patients. No other investigation proved helpful. In only one patient were the findings of more than one investigation diagnostic, and in only 16 of 31 patients treated surgically was the definitive diagnosis made before operation.

In the present series, the patient sample was demographically similar to that in previous reports, representing a predominantly elderly population. Most patients had secondary volvulus, usually due to hiatus hernia, and most presented acutely with epigastric pain, vomiting or upper gastrointestinal haemorrhage. The majority of patients treated surgically underwent a concurrent Nissen fundoplication. This treats concurrent gastro-oesophageal reflux, which may be a problem in patients with an underlying hiatus hernia, as well as 'plugging' the hiatus and thereby reducing the risk of later recurrence. The fundoplication may have contributed to early postoperative dysphagia in some patients, but this always settled spontaneously and it is likely that it helped to achieve a good long-term outcome.

In this series, since 1996 there has been a shift towards laparoscopic surgery and, after two early conversions because of technical difficulties, only one laparoscopic operation has been converted to an open procedure. This was because of adhesions. However, it is important to note that laparoscopic repair of gastric volvulus can be technically demanding, and before reliably dealing with this problem laparoscopically nearly 400 laparoscopic fundoplications had been completed.

Without a prospective randomized controlled trial, it is difficult to compare the outcome of laparoscopic *versus* open surgery. However, in this series there appeared to be

fewer complications and there was a significant reduction in hospital stay in the laparoscopic group. It may therefore be possible to treat more patients with chronic gastric volvulus surgically, including elderly patients with significant comorbidity, who would previously have been treated conservatively. From this series, one might argue that because none of the patients treated conservatively presented with problems surgical intervention is not required. However, because of the risk of future strangulation and death associated with the conservative management of gastric volvulus, where possible patients should be offered surgery as the morbidity of laparoscopic repair is now low.

In summary, gastric volvulus is an uncommon but potentially fatal surgical emergency. If suspected, a contrast study is likely to be of much greater value than any other investigation, including endoscopy. Laparoscopic repair of both acute and chronic volvulus is feasible but can be a surgical challenge, even for those experienced in this field.

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Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland

The following abstracts were presented at the annual scientific meeting of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland on 23–24 September 1999.

The *British Journal of Surgery* prize was awarded to

the abstract entitled 'Pattern of recurrence following subtotal oesophagectomy with two field lymphadenectomy' by S. M. Dresner, J. Wayman, J. Shenfine, A. Harris, N. Hayes and S. M. Griffin.

Laparoscopic splenectomy: a suitable technique for children and adults

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Aims: Splenectomy retains an important role in the management of certain haematological conditions that fail to respond to conventional medical therapy, and has traditionally been performed through a midline or left subcostal incision with patients requiring 5–7 days in hospital. The well recognized benefits of laparoscopic surgery should also apply to splenectomy. This study aimed to develop a safe and effective technique suitable for all age ranges and without the requirement for expensive stapling devices.

Methods: An operative technique evolved over the 5-year period from 1994, from an initial six-port approach with the patient supine, to a four-port approach in a modified right lateral position, with locking surgical clips applied down a 5-mm port to vessels in the hilum, and removal of the spleen within a retrieval bag through a 4–6-cm Pfannanstiel incision. Data were collected prospectively for all patients undergoing laparoscopic splenectomy at Leicester Royal Infirmary, including demographic details, indication for surgery, duration of surgery, length of inpatient stay, transfusion requirement, postoperative complications and the response of the original condition to surgical intervention.

Results: A total of 40 patients underwent laparoscopic splenectomy (14 children, 26 adults) for a variety of conditions (idiopathic thrombocytopenia (ITP) ($n = 24$), haemolytic anaemia ($n = 9$) or malignancy ($n = 7$)) with a median operating time of 180 min for the first 20 patients and 100 min for the second 20 ($P < 0.0001$), and median inpatient stay of 3 days for the first 20 patients and 2 days for the second 20 ($P < 0.0003$). None of the operations was converted to open surgery, five patients required blood and/or platelet transfusion perioperatively, none of the patients had major postoperative complications, 23 of the 24 patients with ITP developed normal platelet counts after operation, and all nine patients with haemolytic anaemia maintained a normal haemoglobin concentration after operation.

Conclusions: Laparoscopic splenectomy can be performed safely and effectively in adults and children without the need for stapling devices.

Increase in the incidence of oesophagogastric carcinoma in the South Thames region: an epidemiological study

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Aims: There is some evidence to indicate that the incidence of gastric and oesophageal carcinoma is changing rapidly in the West. However, to study the true magnitude of the problem (to help in planning health and cancer strategies over the next decades), this epidemiological study was performed.

Methods: The Thames Cancer Registry database for the years 1960–1995 was searched for all oesophageal and gastric cancers in the South Thames region, and was analysed for all subsites for both sexes separately. Statistical analysis using the age-standardized ratio (ASR) (world) and χ^2 test for trend for each subgroup was performed.

Results: The overall incidence of carcinoma of the oesophagus for both sexes saw a marked rise in the period studied, while the overall incidence of gastric cancer fell. In the upper two-thirds of the oesophagus, the increase in incidence was more dramatic for women (from 0.30 in 1960 to 0.70 in 1996; $\chi^2_{\text{trend}} = 18.7$, $P = 0.00015$) than men (from 0.59 in 1960 to 1.09 in 1996; $\chi^2_{\text{trend}} = 4.4$, $P = 0.0354$). In the lower third of the oesophagus, there was a rise in men (ASR from 0.93 in 1960 to 3.43 in 1996; $\chi^2_{\text{trend}} = 466.3$, $P < 0.0001$) as well as in women (ASR from 0.42 in 1960 to 0.91 in 1996; $\chi^2_{\text{trend}} = 51.4$, $P < 0.0001$). For the gastric cardia, the incidence in men increased (ASR from 1.24 in 1960 to 2.41 in 1996; $\chi^2_{\text{trend}} = 109.8$, $P < 0.0001$), while in women it remained unchanged (ASR from 0.33 in 1960 to 0.55 in 1996; $\chi^2_{\text{trend}} = 0.0$, $P = 0.8281$). The incidence of distal gastric carcinoma has decreased in men (ASR from 2.47 in 1980 to 0.63 in 1996; $\chi^2_{\text{trend}} = 264.7$, $P < 0.0001$) and women (from 1.14 in 1980 to 0.43 in 1996, $\chi^2_{\text{trend}} = 131.8$, $P < 0.0001$). For cancers of other subsites of the stomach (fundus, lesser and

greater curvature, and body), there was a fall in incidence in both sexes.

Conclusions: There has been a twofold to threefold increase over 36 years in the incidence of cancer of the oesophagogastric junction with a decreasing incidence in the distal stomach. There was also an increase in the incidence of upper oesophageal cancers, and a decrease in the incidence of cancers of other subsites of the stomach. Studies to cope with this increase and resources to cope with the treatment of these patients are required.

Current nature and management of cancer of the oesophagus and cardia

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Aims: To inform the debate about upper gastrointestinal cancer care in the UK, the incidence of cancer of the oesophagus and cardia (OGJ) was determined in the West Midlands, a region covering 10 per cent of England and Wales, with particular reference to the methods of treatment.

Methods: The case-notes of 2776 patients diagnosed with oesophageal and OGJ cancer in the 5 years from 1 January 1992 to 31 December 1996 were scrutinized by one experienced surgeon. Tumour types were classified by histology and site, and treatment modalities assessed for 30-day mortality rate together with life-table analyses.

Results: Oesophageal cancer was identified in 2188 patients (61 per cent lower, 34 per cent middle, 4 per cent upper), including 999 squamous carcinomas (27 per cent lower, 64 per cent middle, 9 per cent upper) and 995 adenocarcinomas (97 per cent lower, 3 per cent middle), while there were 588 cases of OGJ cancer (94 per cent adenocarcinomas). Resection was the commonest treatment (865 cases, 31 per cent), with a mortality rate of 10 per cent for oesophageal and 4 per cent for OGJ cancer. Palliative resection had a higher mortality rate than radiotherapy (9 versus 3 per cent), compared with 22 per cent for endoscopic palliation, while the 30-day mortality rate was 30 per cent for the 308 patients given no treatment.

Conclusions: Squamous carcinomas and adenocarcinomas of the oesophageal body are now equally common; lower-third and OGJ tumours are predominantly adenocarcinomas. This study provides baseline data for critical appraisal of potential changes in the delivery of upper gastrointestinal cancer in the UK.

Early results of laparoscopic Swedish adjustable gastric banding for morbid obesity

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Aims: Gastric bypass and vertical banded gastroplasty (VBG) are currently the most commonly performed bariatric proce-

dures but neither are ideal. The results of the first 56 patients who had laparoscopic Swedish adjustable gastric banding (SAGB) are presented.

Methods: All patients referred for bariatric surgery were considered for SAGB. Each was given the alternative of gastric bypass. Patients with a body mass index of less than 35, large hiatus hernia, under 18 years of age, gastric pathology and significant psychiatric illness were excluded. Preoperative gastroscopy, ultrasonographic examination of the gallbladder and specialist anaesthetic assessment were arranged. All but five patients had attempted laparoscopic procedures. Patients were discharged when they were mobile and could tolerate 1500 ml fluid per day. Patients were given a liquidized diet for 6 weeks. Assessments were made at 6 weeks and 3, 6, 9 and 12 months.

Results: Some 56 consecutive patients were followed for up to 12 months. The conversion rate fell from 52 per cent for the first 25 patients to 20 per cent for the last 20. Conversion rates were higher in men and in superobese patients. The duration of a laparoscopic operation fell significantly with experience but was still significantly longer than that of an open procedure ($P < 0.004$). The length of hospital stay was significantly shorter for laparoscopic procedures ($P < 0.001$). There was no death and little morbidity. Two bands had to be removed (easily) by open surgery, one for infection and one for a recurrence of gastric herniation. The mean excess weight loss was 60 per cent at 12 months. Greater than 50 per cent of excess body-weight was lost by 48 per cent of patients at 6 months and 69 per cent at 12 months. Band adjustments in most patients achieved further weight loss to compensate for late pouch dilatation. Most failures were in patients who failed to attend.

Conclusions: SAGB appears to have many advantages over gastric bypass and VBG; it avoids stapling the stomach, should not cause any malabsorption, can be performed laparoscopically, is adjustable, is more readily reversed (if necessary) and, therefore, has the potential for lower associated morbidity and mortality rates. In terms of excess weight loss, the early results are certainly as good, if not better, than those of gastric bypass and VBG.

Pattern of recurrence following subtotal oesophagectomy with two field lymphadenectomy

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Aims: Despite increasingly radical surgery for oesophageal cancer many patients continue to represent with recurrent disease. This study aimed to evaluate the pattern of failure following attempted curative oesophagectomy with mediastinal and upper abdominal lymphadenectomy.

Methods: Some 212 consecutive patients undergoing R₀ resection for malignancy between 1 April 1990 and 1 April 1999 were followed up for evidence of recurrence. Clinical evaluation was supported by ultrasonography, computed

tomography, isotope scan, endoscopy and laparotomy with biopsy assessment if appropriate. Patients were excluded if recurrence was diagnosed on clinical grounds alone. Statistical analysis was performed using χ^2 and log rank tests.

Results: Some 142 patients with adenocarcinoma and 70 with squamous carcinoma (SCC) were followed up for a median of 14 (range 1–108) months. Sex and age distribution were similar for both histological subtypes (men : women 3 : 1, median age 64 (30–79) years). Twenty patients died from non-cancer related causes, including 11 (5 per cent) from postoperative complications. Some 89 patients (42 per cent) developed proven recurrent disease of which seven are alive and 82 dead. The median time to recurrence was 11 (2–40) months with a median time to death thereafter of 3 (1–21) months. The pattern of recurrence was locoregional in 23 per cent (oesophageal bed 15 per cent, upper abdominal 3 per cent, upper mediastinal 3 per cent, cervical 2 per cent) and haematogenous in 18 per cent (comprising liver 8 per cent, bone 4 per cent, cerebral 3 per cent, lung 2 per cent, skin 1 per cent) with peritoneal dissemination in 1 per cent. While there was no difference in the overall pattern of dissemination for each histological subtype, the incidence of cervical and upper mediastinal recurrence was significantly higher for adenocarcinoma compared with SCC ($\chi^2 = 5.9$, 1 d.f., $P < 0.02$). The timing of recurrence was similar for both histological subtypes: 60 per cent of all recurrence occurred within 12 months of surgery, with distant and locoregional recurrence occurring at a median of 10 (2–40) and 11 (2–32) months respectively.

Conclusions: The low incidence of upper mediastinal and cervical recurrence suggests that more extensive lymphadenectomy is unlikely to impact upon survival. Improved staging modalities are required to identify the significant number of patients who develop early recurrence in the first year following surgery in order to offer them multimodality therapies of non-surgical palliation.

Management of spontaneous rupture of the oesophagus

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Aims: Spontaneous rupture of the oesophagus (SRO) is a rare and often fatal event. The aim of this study was to evaluate the presentation, management and outcome of SRO in a single unit.

Methods: Data were collected on all patients presenting with SRO over a 5-year period with respect to presenting features, diagnostic investigations and subsequent management. Statistical analysis was by Student's *t* test, χ^2 and Fisher's exact tests.

Results: Fourteen patients were identified, 12 men and two women with a median age of 64 (range 18–78) years; eight were tertiary referrals. Thirteen of 14 patients presented with chest or upper abdominal pain following vomiting or retching and 13

had an abnormal initial chest radiograph; only one presented with Mackler's triad of pain, vomiting and surgical emphysema. The median delay to diagnosis was 21 (range 1–84) h; this delay did not significantly affect outcome ($P = 0.16$). An endoscopic assessment and contrast swallow were performed in all patients. Nine of ten patients with a demonstrable leak and full-thickness tear were managed surgically and the four patients with no leak were managed conservatively ($P = 0.005$); surgical management consisted of thoracotomy, lavage, repair of the perforation and a feeding jejunostomy. Seven patients had a repair over a T tube and two had a primary repair. All conservatively managed patients had contained, controlled or intramural perforations and two also required a feeding jejunostomy. Patients requiring surgery had a longer hospital stay (mean(s.d.) 57.9(34.8) versus 22.2(30.7) days; $P = 0.081$) and a significantly longer intensive care unit stay ($P = 0.044$). The overall mortality rate from SRO was 14 per cent (two patients); no deaths occurred in the conservatively managed group.

Conclusions: SRO continues to be diagnosed late despite a classical history and/or abnormal chest radiograph. Endoscopic assessment of perforations is safe and in combination with a contrast swallow can confidently predict patients with contained or controlled rupture in whom non-operative management is successful.

Achalasia: management, outcome and surveillance in a specialist unit

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Aims: The management and surveillance of achalasia remains controversial at the present time. The aim of this study was therefore to evaluate the results of endoscopic management and subsequent surveillance of patients with achalasia presenting to a specialist unit.

Methods: A prospective cohort of 40 patients with a radiological and manometric diagnosis of achalasia who presented to this unit between 1991 and 1998 were studied; the male : female ratio was 1 : 1 and the median age 38 (range 15–84) years. Twenty-one patients presented *de novo*, seven had previously undergone cardiomyotomy and 12 were referred following unsuccessful dilatation.

Results: Some 36 patients were treated with balloon dilatation (Microvasive achalasia balloon, 35/40 mm). Results were graded 1–4 (1, asymptomatic; 2, symptomatic but significantly improved; 3, symptomatic with no change; and 4, symptomatic but worse); 29 of 36 patients were grade 1 at subsequent follow-up and the remaining seven were grade 2 (median follow-up 17 (range 5–96) months). There was a single complication of oesophageal perforation which was treated conservatively with full recovery. Following intervention, patients were enrolled in a prospective surveillance programme of chromoendoscopy at 2-year intervals; in a total of 74 patient-years' follow-up, two

superficial squamous cell carcinomas (SCCs) and one adenocarcinoma (following cardiomyotomy) were detected, giving a relative risk of one cancer in 25 patient-years.

Conclusions: Balloon dilatation is a safe and effective treatment for achalasia even in patients who have had previous unsuccessful dilatations or cardiomyotomy. There is a high risk of SCC and the adenocarcinoma may have resulted from previous refluxogenic therapy, so all patients with achalasia should be followed up with surveillance endoscopy.

Prognostic value of quality of life scores in patients with oesophageal cancer

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Aims: Quality of life (QL) data are useful in evaluating treatment, in screening or psychosocial morbidity and there is accumulating evidence to show that they predict survival. This study investigated if baseline QL scores are prognostic for patients with oesophageal cancer.

Methods: Between 1993 and 1995, 89 consecutive new patients with oesophageal cancer completed baseline QL assessments with the EORTC QLQ-C30 questionnaire and the dysphagia scale from the oesophageal cancer module. Cox's proportional hazards models were used to assess the impact of QL variables on survival (82 patients have died).

Results: Univariate analyses revealed that better baseline physical and role function scores were significantly associated with increased survival ($P \leq 0.001$) and worse fatigue, appetite loss and constipation scores were significantly associated with shorter survival ($P < 0.01$). Multivariate analysis, taking account of associations between the QL scores and adjusting for age, tumour node metastasis classification T, N and M stage, showed that only physical function at baseline remained significantly associated with survival ($P = 0.002$); adjusting for sex, histology and comorbid disease did not alter the findings.

Conclusions: There is evidence to suggest that QL parameters may be important prognostic factors for patients with oesophageal cancer. Stronger evidence may be gained from a more highly powered study, and further understanding of the associations between QL variables and clinical data is needed.

Development of an EORTC module to improve quality of life assessment in patients with gastric cancer

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Aims: A valid measure of quality of life (QL) that is sensitive to clinically significant changes in health is important for the assessment of patients with gastric cancer. The aims of this study were to examine whether the EORTC (European Organisation for Research and Treatment of Cancer) QLQ-

C30 core questionnaire alone could distinguish between two clinically different groups of patients and to design a module, which included relevant patient-defined gastric cancer-specific variables.

Methods: The QLQ-C30 was completed by patients with potentially curable disease and those undergoing palliative treatment, and the results were compared between the two groups. A disease-specific module was then developed in four distinct phases according to EORTC guidelines. Relevant issues were identified from a literature search and structured interviews with patients and healthcare professionals, and worded into a provisional questionnaire which was pretested to determine any problems in its content, before formal validation.

Results: All of the subscales and single items within the QLQ-C30 were scored similarly by 144 patients, 86 with operable disease and 58 having palliative treatment, except constipation ($P = 0.001$). On the basis of interviews with 58 patients and 24 professionals, from the UK, France, Germany and Spain, 43 issues were reduced to produce a provisional questionnaire consisting of 24 items and pretested in 114 patients undergoing radical gastrectomy, palliative resection or other supportive measures. The resulting questionnaire, containing 22 items divided into five scales (dysphagia, pain, reflux, dietary restrictions and specific emotional problems related to gastric cancer and its treatment) and four single items, is undergoing validation.

Conclusions: The EORTC QLQ-C30 is a valid generic instrument, but does not address all factors constituting QL in patients with gastric cancer. A specific module has been developed, which includes issues volunteered by patients to increase sensitivity and improve the evaluation of treatments for a disease where QL is important.

Association of tumour necrosis factor microsatellite haplotypes with chronic pancreatitis

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Aims: Recent evidence implicates the immune system in having a primary pathogenic role in the development of chronic pancreatitis (CP). This study examined the relationship between the tumour necrosis factor (TNF) gene and susceptibility to CP.

Methods: DNA was extracted from the blood of 40 patients with CP, 107 ethnically matched normal controls and 33 patients with alcohol-induced liver disease (alcoholic controls). Three microsatellite polymorphisms at the TNF locus were examined by the polymerase chain reaction, gel electrophoresis and autoradiography.

Results: The TNFa6 allele was significantly over-represented in patients with CP compared with normal controls ($\chi^2 = 4.09$, $P = 0.043$), and in those with alcoholic CP ($n = 24$) compared with alcoholic controls ($\chi^2 = 4.63$, $P = 0.031$). The three locus

haplotypes 6-5-1 and 2-5-2 were significantly over-represented ($\chi^2 = 4.14$, $P = 0.042$) and under-represented ($\chi^2 = 4.63$, $P = 0.042$) respectively in patients with alcoholic CP compared with alcoholic controls.

Conclusions: A TNF haplotype has been defined that is associated with CP. This is consistent with a genetically determined role for TNF in the immunopathogenesis of CP.

Mismatch between trainees' subspecialist interest and advertised jobs; worrying implications for upper gastrointestinal trainees

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Aims: The aim of this study was first to assess the primary subspecialist interests of general surgical specialist registrars who were accredited and still looking for a consultant position, or who were within 3 years of their CCST (certificate of completion of surgical training). These interests were then compared with subspecialist interests declared in consultant vacancies advertised in the *British Medical Journal* over the preceding 16 months.

Methods: All trainees in general surgery holding a national training number in six regions (Mersey, North West, Trent, Yorkshire, Northern, West Midlands) were identified, and those accredited or within 3 years of their CCST ($n = 136$) were telephoned to ascertain their primary subspecialist interest, whether they had a higher degree and what their desired consultant job would be. The consultant vacancies advertised in the *British Medical Journal* between 3 January 1998 and 8 May 1999 were assessed according to the required subspecialist interest.

Results: Upper gastrointestinal surgery is the second most popular subspecialty ($n = 37$; 27 per cent of trainees) after colorectal surgery ($n = 40$; 29 per cent of trainees). However, there were fewer consultant vacancies in upper gastrointestinal surgery (31 of 226; 14 per cent of jobs) than in any of the other three main subspecialist areas of general surgery (colorectal, vascular and breast/endocrine). The ratio of percentage of jobs to percentage of trainees was lowest in upper gastrointestinal surgery (0.50), compared with colorectal (0.77), vascular (0.89) and breast/endocrine (2.23) surgery.

Conclusions: Upper gastrointestinal surgery appears to be the most competitive of the general surgical subspecialties at present, having by far the lowest ratio of jobs to trainees. In addition, 87 per cent of upper gastrointestinal trainees have or are completing a higher degree, and 43 per cent expressed a desire to work in a teaching hospital.

Prospective 5-year audit for day-case laparoscopic cholecystectomy

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Aims: Laparoscopic cholecystectomy can be performed as a day-case procedure but success depends on adequate recovery

time, patient motivation and physical condition. To determine the proportion of patients suitable for a day-case procedure, 23-h stay and inpatient treatment, a prospective audit was introduced in 1994.

Methods: A 5-year (1994–1999) prospective annual audit was performed for all patients undergoing laparoscopic cholecystectomy (537 patients). In the first 3 years patients were either classified as day-case or inpatient stay; the establishment of a 23-h stay ward allowed a third option for these patients.

Results: Day-case laparoscopic cholecystectomy, including 23-h stay in the final 2 years of the audit, increased in each of the 5 years from 16 to 80 per cent. The audit loop was closed when the successful allocation rate for day-case patients was reaudited; this increased from 56 per cent in the first year to 88 per cent in the final year.

Conclusions: This audit has identified the need for extended recovery for patients undergoing more major procedures on an ambulatory basis such as laparoscopic cholecystectomy. Further refinements in selection criteria and improved analgesia control are needed to reduce the unexpected extended stay for day-case and ambulatory patients.

Current practice in the management of acute cholecystitis

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Aims: Several recent papers have advocated emergency cholecystectomy for patients with acute cholecystitis, stating that it is safe, cost effective and leads to less time off work. This study was designed to assess current practice in the management of acute cholecystitis in the UK.

Methods: A postal questionnaire was sent to 357 consultant surgeons who were thought to be involved in a general surgical on-call rota, to ascertain their current management of patients with acute cholecystitis. Replies were received from 250 consultants (70 per cent) of whom 242 (68 per cent) were involved in a general surgical take. Sixteen of these consultants, however, handed their patients with acute cholecystitis on to a different team the following day for further management.

Results: Twenty-seven consultants (12 per cent) routinely treat their patients by emergency cholecystectomy whenever possible, with 24 stating that they would do this within 72 h. Limiting factors to this practice were stated to be availability of surgical staff (15), theatre space (nine) and radiological investigations (four). The remaining consultants ($n = 199$) routinely manage their patients conservatively initially and providing they settle, either (1) book directly for cholecystectomy ($n = 94$, 47 per cent), (2) reassess as an outpatient ($n = 65$, 33 per cent), (3) either of above ($n = 21$; 11 per cent) or (4) refer on to a colleague ($n = 19$, 10 per cent). The commonest indications for acute cholecystectomy stated by consultants whose initial treatment policy is conservative are spreading peritonitis due to bile leak (93 per cent), empyema (89 per cent), unexpected space on a theatre list (28 per cent) and failure of an acute episode to settle (21 per cent). The laparoscopic method is the commonest for both elective and emergency cholecystectomy,

but the percentage of consultants using an open method rises dramatically from 9 per cent in the elective situation to 48 per cent for emergency cholecystectomy.

Conclusions: Despite evidence to support the increased use of emergency cholecystectomy, this practice is routinely carried out by only 12 per cent of consultants. However, of the consultants who treat their patients conservatively, 28 per cent are prepared to undertake emergency cholecystectomy if an unexpected space appears on the theatre list.

Extending the indications for curative liver resection by portal vein embolization

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Aims: The aim of ipsilateral portal vein embolization is to induce hypertrophy of normal tissue when resection of a cancerous portion of the liver is contraindicated only by the volume of liver that would remain following surgery. This study reports its use in primary and metastatic liver tumours.

Methods: Eight patients with inoperable liver tumours (three women and five men of median age 68.5 years; three colorectal hepatic metastases, two cholangiocarcinomas and three hepatocellular cancers) were selected for portal vein embolization. Selected portal branches were occluded distally with microbeads and proximally with coils. Liver volumes were determined by magnetic resonance imaging before embolization and again before surgery, 6–8 weeks later.

Results: Embolization was performed successfully in seven patients by the percutaneous-transhepatic route; one further patient required an open cannulation of the inferior mesenteric vein. Management was altered in six patients, who proceeded to 'curative' surgery. The projected remaining (predominantly left lobe) liver volumes increased significantly from a median of 350 to 550 ml ($P < 0.05$, Wilcoxon matched pairs test). Two patients had disease progression such that surgery was no longer indicated. One patient, whose disease progressed, had the left portal branch occluded unintentionally by a misplaced coil that was successfully retrieved, although the left portal branch remained occluded.

Conclusions: Portal vein embolization produced significant hypertrophy of the normal liver and extended the option of 'curative' surgery to six of the eight patients in whom it was attempted. It appears to be equally effective for primary and metastatic liver tumours in selected patients.

Experience of pancreaticoduodenectomy in a district general hospital

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Aims: Long-term survival after surgery for pancreatic cancer remains very low and it is particularly important that minimal

surgery-related morbidity and mortality rates are achieved. It has been stated that centres performing small numbers of proximal pancreaticoduodenectomies are likely to have high morbidity and mortality rates. The results of pancreatic surgery in a district general hospital are reported.

Methods: This was a retrospective analysis of all pancreaticoduodenectomies over 4 years.

Results: Twenty-one selected patients underwent proximal pancreaticoduodenectomy and two patients total pancreatectomy over a 4-year period from 1995 to 1999. The operations were performed by two surgeons with a special interest in upper gastrointestinal surgery. The median age was 62 (38–83) years. There were 14 men and nine women. Fifteen patients had adenocarcinoma of the head of the pancreas, five had ampullary carcinoma, one duodenal carcinoma and there was one case of chronic pancreatitis. Six patients had pylorus-preserving pancreaticoduodenectomy (PPPD) and 15 had a standard Whipple procedure. The median stay in hospital was 20 (13–26) days. Two patients had a pancreatic leak, one of whom developed an intra-abdominal abscess which was treated successfully by percutaneous drainage. Six patients experienced delayed gastric emptying, two of whom had PPPD. Both the 30-day and in-hospital mortality rates were zero. The median number of lymph nodes dissected was 12 and in 11 patients no nodal metastasis was found.

Conclusions: It is possible to perform pancreatic surgery in a district general hospital and achieve results that are comparable to those of specialist centres.

Portal vein thrombosis following splenectomy

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Aims: The aim of this study was to assess the risk and progress of portal vein thrombosis (PVT) after splenectomy.

Methods: A prospective study was conducted in which two groups of patients were compared; each group comprised 50 patients (27 men, 23 women). Patients in the splenectomy group were of mean age 46.3 years. A second group of patients (mean age 48.5 years) had upper abdominal surgery other than splenectomy. All patients were examined before and 2 weeks after operation by duplex Doppler ultrasonography (DDUS) of the portal system. Those who developed PVT were followed up by DDUS at 6 and 12 months.

Results: PVT developed in 10 per cent of patients who underwent splenectomy. The portal vein was completely occluded by thrombus in 4 per cent and partially occluded in 6 per cent of patients. Symptoms and signs attributable to PVT (abdominal pain, diarrhoea, nausea, vomiting and mild fever) were found in 80 per cent of those who developed this complication. Follow-up of such patients revealed complete recanalization of portal vein in 40 per cent and partial recanalization in 60 per cent after treatment with antibiotics and long-term anticoagulation therapy. No patient who

underwent upper abdominal surgery (other than splenectomy) developed PVT afterwards.

Conclusions: Splenectomy (compared with other upper abdominal surgery) is followed by PVT in 10 per cent of patients but can be treated successfully.

Operative versus conservative management of adhesional intestinal obstruction

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Aims: This prospective controlled trial was undertaken to resolve the controversy over whether intestinal obstruction due to postoperative adhesions should be managed by immediate operation or by conservative care.

Methods: A randomized prospective controlled study was undertaken of all private and public sector patients admitted under the care of one surgeon with intestinal obstruction due to postoperative adhesions over a 15-year period. The patients were randomly allocated either to immediate operation or conservative care with nasogastric aspiration and intravenous fluids. Patients managed conservatively who had not settled after 5 days were operated on. The data were analysed by Student's *t* test and Fisher's exact test.

Results: There were 127 patients. The two groups were statistically identical regarding age, number of previous operations and time since last operation, and heart rate, blood pressure, haemoglobin concentration, white count and urea level on admission. Sixty-three patients were treated conservatively; 22 failed to settle and were operated on, of whom 11 required a bowel resection. There were two postoperative deaths. In 64 patients treated immediately by operation, the incidence of bowel resection was not significantly reduced (22 per cent; $P > 0.05$) but there were four postoperative deaths. There was no significant difference in the length of stay.

Conclusions: Conservative management of postoperative adhesional intestinal obstruction is safe and 65 per cent settle. In those who fail to settle there is no significantly increased risk of bowel strangulation. There is no way of identifying those who will not settle from the history or initial investigations on admission.

Early outcome after laparoscopic and open floppy Nissen fundoplication

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Aims: There remains debate regarding the best operative procedure for gastro-oesophageal reflux. For those who advocate a full 'floppy' Nissen fundoplication there is some scepticism that this can be completed effectively laparoscopically with division of all the short gastric vessels. This study therefore compared the results of patients operated on in two

different hospitals in which floppy Nissen fundoplication was carried out either laparoscopically (hospital 1) or by open surgery (hospital 2).

Methods: All patients undergoing antireflux surgery in both hospitals were recorded prospectively and perioperative data were collected retrospectively from the case records. A postoperative questionnaire was sent to each patient to determine the modified DeMeester score and the impact of surgery on daily activities, which were then analysed anonymously by an independent clinician.

Results: Operating time was significantly longer (median 150 versus 75 min; $P < 0.001$), but postoperative stay (2 versus 4 days; $P < 0.001$) and return to normal activities (14 versus 25 days; $P < 0.002$) were shorter for the laparoscopic approach. There was no difference in gas bloat (both groups median 1.0, range 0–3), dysphagia (median 1.0 versus 0.0, range 0–3) or modified DeMeester score (both groups median 1.0, range 0–9) between the two techniques (median follow-up 10 and 15 months).

Conclusions: As the postoperative results were comparable this study confirms that a 'floppy' Nissen fundoplication with complete mobilization of the gastric fundus can be performed laparoscopically. The advantages of a shorter hospital stay and earlier return to normal activities are offset by a longer operating time.

Telementoring in laparoscopic cholecystectomy: a useful adjunct in training and assessment of higher surgical trainees

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Aims: This study assessed the feasibility, safety and utility of telementoring as a training tool in laparoscopic cholecystectomy (LC) for higher surgical trainees (HST). Telementoring in LC was developed as a technique for objective assessment of performance and progress in order to help decide when an HST is competent to perform LC unsupervised.

Methods: This was a prospective study of patients attending for LC, with surgery performed by an HST, in which the laparoscopic image was relayed live to an adjoining room where a supervising consultant observed the procedure. The trainee or supervisor sought or proffered advice/assistance as appropriate, and safety, complication rates, operating time, difficulty of procedure, intervention rate and type were recorded.

Results: LC was accomplished in 33 of 34 patients enrolled; there was one conversion to an open procedure. Interaction between the HST and trainer occurred in 11 cases, by way of advice being sought or offered, and in two of these the supervisor scrubbed up and took over the operation. The rate of interaction and duration of the procedure increased with procedure difficulty, with rates of interaction for difficulty grades 1, 2 and 3 of 15 per cent (two of 13), 41 per cent (seven of 17) and 50 per cent (two of four), and overall median operating times of 35 (23–50), 45 (28–75) and 92 (45–110) min respectively.

Conclusions: Telementoring for trainees capable of performing LC is feasible and appears to be safe with a supervising surgeon situated in the immediate vicinity. Telementoring in LC is a promising tool that may provide objective assessment of a trainee's insight, skill and progress in operative performance.

Management of acute pancreatitis: a comparative audit of clinical practice against the recommendations of the British Society of Gastroenterology

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Aims: In 1998 the British Society of Gastroenterology (BSG) published national guidelines for the management of acute pancreatitis (AP) in an attempt to improve diagnosis and reduce mortality rates. A comparative audit was undertaken of the management of AP against the BSG recommendations.

Methods: A retrospective analysis of 53 patients (median age 61 (range 24–95) years) admitted with AP during 1998 was undertaken and a comparison was made with the BSG guidelines.

Results: Some 70 per cent ($n = 37$) of the patients were admitted with mild AP and 30 per cent ($n = 16$) with severe AP. The BSG recommendations are shown in parentheses in the following text. The overall mortality rate was 17 per cent (less than 10 per cent), zero in mild AP and 56 per cent in patients with severe AP (less than 30 per cent). A correct diagnosis of AP was made within 48 h of admission in all patients (100 per cent). Severity stratification within 48 h using the Glasgow criteria and C-reactive protein (CRP) level, as suggested by the BSG, was done in approximately 80 per cent of patients.

	Matched criteria (%)							
	WCC	Glucose	Urea	PaO ₂	Calcium	Albumin	LDH	ALT
On admission	100	94	100	81	89	89	47	51
After 48 h	98	66	98	51	87	91	32	89

PaO₂, arterial partial pressure of oxygen; WCC, white cell count; LDH, lactate dehydrogenase; ALT, alanine aminotransferase

CRP was measured in 51 per cent of the patients within the first 4 days (100 per cent) and at the end of the first week (100 per cent). Gallstones and alcohol counted for 72 per cent of causes of AP and the aetiology was determined in 77 per cent (75–80 per cent). All patients with severe AP were managed in a high-dependency or intensive therapy unit with central venous pressure monitoring and prophylactic intravenous antibiotics, and underwent dynamic computed tomography within 3–10 days of admission (100 per cent). Some 86 per cent of patients with suspected common bile duct (CBD) stones (jaundice,

deranged liver function tests, dilated CBD) underwent endoscopic retrograde cholangiopancreatography with or without duct drainage and clearance.

Conclusions: Management of AP closely mirrors the BSG guidelines, but fails to fully address severity stratification with respect to LDH, CRP and PaO₂ at 48 h. A thorough analysis of patients with severe AP (i.e. extent of pancreatic necrosis, onset of infection) has been undertaken to explain the mortality rate and it is proposed to prospectively audit admissions with AP in 1999 in order to close the audit loop.

Symptoms are a poor indication of severity of reflux in Barrett's oesophagus

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Aims: Patients with Barrett's oesophagus have increased acid and duodenogastric reflux and impaired motility compared with non-Barrett's patients with reflux disease. Impaired sensitivity to acid infusion and distension have also been described, but the relationship of this visceral response to symptoms is unclear. A symptom index was used to compare Barrett's and non-Barrett's patients with reflux.

Methods: Patients with reflux (DeMeester score above 14) were studied with 24-h pH monitoring and manometry. An event marker recorded symptom events. An event was positive if it corresponded to a period greater than 10 s within 2 min either side of the drop in pH. The symptom index was calculated as the number of symptoms with pH less than 4/total number of symptoms $\times$ 100.

	Acid score	Symptom index (%)	Motility disturbance (%)
Non-Barrett's	41 (17–137)	52 (0–100)	22
Barrett's	70 (12–194)	0 (0–100)*	56†

Values are median (range). * $P < 0.01$, † $P < 0.05$ (Wilcoxon and χ^2 tests)

Results: Eighteen patients with Barrett's oesophagus were compared with 58 non-Barrett's patients with significant reflux.

Conclusions: Patients with Barrett's oesophagus have a low symptom index compared with non-Barrett's patients with reflux disease. This occurs despite a near 100 per cent increase in acid exposure in the Barrett's group. Symptoms are thus no guide to the severity of reflux in patients with Barrett's oesophagus. Proof of efficacy of therapeutic modalities may need physiological rather than symptom-based confirmation.

Acute severe pancreatitis and multiple organ failure: total parenteral nutrition is still required in a proportion of patients

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Aims: Enteral nutrition (EN) is increasingly advocated as the favoured means of nutritional support in patients with multiple organ failure resulting from acute severe pancreatitis. In a proportion of patients, however, EN may not be feasible either because of gastrointestinal stasis and high nasogastric aspirates or because of superseding complications of pancreatitis such as fistulation. In these cases total parenteral nutrition (TPN) is indicated.

Methods: Patients with acute severe pancreatitis admitted to the intensive care unit (ICU) were commenced on either nasogastric or, where established, jejunostomy EN. Rates of EN were controlled by protocol and volumes of nasogastric aspirate. TPN was commenced when volumes of EN were persistently inadequate or when this route was contraindicated (e.g. high-volume small bowel fistula). Physiological and outcome data were collected prospectively and included severity of illness scoring (Acute Physiology And Chronic Health Evaluation (APACHE) II), length of stay, duration of EN and TPN, and hospital outcome.

Results: Of 69 patients with acute severe pancreatitis, 31 were transferred from other ICUs. The median APACHE II score was 18 (range 4–40) and the overall hospital mortality rate was 39 per cent. Seventeen patients (25 per cent) were managed with EN alone, ten (14 per cent) with TPN alone and 19 (28 per cent) with a combination of both. Twenty-three (33 per cent) did not have any nutritional support during their ICU stay. The mortality rate was worse among patients who received TPN only than in those who had EN (60 *versus* 24 per cent).

Conclusions: EN is likely to remain the route of choice for nutritional support in the ICU. However, in high-risk patients with acute severe pancreatitis EN may not be feasible and TPN is often required. This may reflect a greater severity of illness.

Long-term symptomatic follow-up after Lind fundoplication

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Aims: Few published studies have detailed the long-term results of antireflux surgery. The aim of this study was to assess the long-term success of open Lind fundoplication in controlling the symptoms of gastro-oesophageal reflux disease.

Methods: One hundred and thirty-two patients with reflux symptoms underwent a primary Lind fundoplication between April 1986 and February 1994; all operations were supervised or performed by one surgeon. The median age at operation was

47 (range 17–77) years. All patients attended for follow-up in the early postoperative period. It was possible to conduct a telephone interview to assess long-term symptom control, at a median time of 9.5 (range 5–13) years following operation, in 112 of the 124 patients who were still alive.

Results: Ninety-one patients underwent oesophageal pH studies before and soon after operation. The oesophageal pH was less than 4 for a mean 14.9 per cent of the time before operation, falling to 2.4 per cent in the early postoperative period ($P < 0.001$, Wilcoxon test). At early postoperative assessment, two patients complained of mild reflux symptoms and 44 (33 per cent) complained of postfundoplication symptoms (dysphagia, epigastric bloating and early satiety). At telephone interview, 106 patients (95 per cent) were symptom free with regard to heartburn and regurgitation. Six patients have developed recurrent reflux symptoms, in four of whom symptoms are controlled by a proton pump inhibitor. Two patients have required further antireflux surgery, one within 2 months of the first procedure for severe dysphagia and the other for recurrent reflux. Significant postfundoplication symptoms persist (dysphagia with or without gas bloat) in three patients (3 per cent).

Conclusions: Open Lind fundoplication appears to be effective in the long-term control of gastro-oesophageal reflux in 95 per cent of patients and represents a standard against which the long-term results of laparoscopic surgery will need to be compared.

Benign anastomotic stricture following transthoracic subtotal oesophagectomy and stapled oesophago-gastrostomy: risk factors and management

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Aims: Benign anastomotic stricture (BAS) is a common cause of dysphagia following oesophagectomy. The aim of this study was to assess the incidence of BAS, identify risk factors for its development and evaluate the results of postoperative endoscopic dilatation.

Methods: A consecutive series of 234 patients undergoing oesophagectomy with a stapled intrathoracic oesophagogastric anastomosis (Autosuture CEEA gun) between April 1990 and April 1999 were studied. BAS was defined as dysphagia with anastomotic narrowing (XQ200 endoscope) and no suspicion of recurrence. Statistical analysis was by the χ^2 and Mann-Whitney U tests.

Results: The postoperative mortality rate was 5 per cent (12 of 234) and the anastomotic leak rate 3 per cent (six of 234). One-third of patients (70 of 222) who survived surgery re-presented with dysphagia; 5 per cent (11 of 222) were found to have proven local recurrence and 27 per cent (59 of 222) BAS. The median time to development of BAS was 92 (range 24–210) days. BAS formation was significantly related to the size of

the staple gun employed: 21 mm, 80 per cent (eight of ten); 25 mm, 32 per cent (25 of 78); 28 mm, 23 per cent (19 of 81); 31 mm, 19 per cent (seven of 37) and 34 mm, 0 per cent (none of five) ($\chi^2 = 18.3$, 4 d.f., $P < 0.01$). All patients underwent radiographically controlled endoscopic dilatation with no complications. Recurrent BAS occurred in over half of these patients (32 of 59), who had a median of 2 (range 2–17) recurrences all resolving within 532 (mean interval 68) days. Recurrent BAS formation was also significantly related to the size of the staple gun employed ($\chi^2 = 11.6$, 4 d.f., $P < 0.05$). Following the introduction of the Autosuture 'ult-top' device in July 1995 the median size of gun used rose from 25 to 28 mm with an overall decrease in the incidence of BAS from 33 to 21 per cent ($\chi^2 = 4.0$, 1 d.f., $P < 0.05$). All patients with anastomotic leaks survived and none subsequently developed BAS. Similarly, no association was found between the development of BAS and the anastomotic site (measured from incisors), tumour subtype, resection margin length, sex, age or preoperative cardiorespiratory status.

Conclusions: Staple gun size is an important risk factor for BAS formation and 'ult-top' devices enable the use of a larger head with a subsequently lower incidence of BAS. Endoscopic dilatation is an effective treatment for BAS which rarely recurs and always resolves within 18 months.

Biliary complications associated with laparoscopic cholecystectomy: analysis of common misconceptions

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Aims: General surgeons often express the view that the majority of biliary complications following laparoscopic cholecystectomy are caused by trainee surgeons; complications occur most often in the presence of difficult anatomy or pathology; biliary injuries occur more proximally in the biliary tree than at open cholecystectomy; most injuries are recognized at the time of surgery; and most complications can be managed non-operatively. The aim of this study was to determine if these views are substantiated in clinical practice.

Methods: Thirty consecutive patients were referred to a specialist hepatobiliary unit over a 7-year period with biliary complications following laparoscopic cholecystectomy. The mode of presentation, management and outcome of these patients were analysed.

Results: In 21 cases the initial operator was a consultant. Four of the 30 complications occurred in the presence of an anatomical variation or unusually difficult pathology. Only patients in whom a previous attempt at repair had been made had injuries at or proximal to the bile duct confluence; the only two deaths occurred in this group. Only 41 per cent of injuries were detected at the time of surgery and 89 per cent required

further surgical intervention, hepaticojejunostomy being the most common procedure performed (75 per cent).

Conclusions: The majority of bile duct injuries are not caused by trainees, do not occur because of unusual anatomy or pathology, do not occur in the proximal biliary tree, are not recognized at the time of the initial operation and often require major reconstructive procedures for their management.

Cholecystectomy: does subspecialization alter workload?

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Aims: Cholecystectomy is a common operation. This study reviewed the changes in workload and practice in a teaching hospital over a 4-year period, during which a hepatobiliary subspecialist unit was developed.

Methods: Computerized demographic data, and details of operations and inpatient events were reviewed for all patients undergoing cholecystectomy in a single teaching hospital from 1993 to 1997. For statistical analysis the consultants were grouped into those with a hepatobiliary interest ($n = 3$) and those with other primary interests ($n = 6$); and the workload for the first 12 months of the study was compared with that of the last 12-month period.

Results: Between April 1993 and April 1997, 1121 cholecystectomies were performed, of which 75 were excluded because they were performed with other simultaneous procedures. Of the remaining operations, 911 involved cholecystectomy alone (mean patient age 52.9 years), and 135 (12.9 per cent) comprised cholecystectomy with exploration of the common bile duct (ECBD) (mean age 60.1 years). Between the first and last years studied, the rate of ECBD rose significantly from 7.4 to 14.9 per cent ($P < 0.01$, χ^2 test), and the proportion of ECBD procedures being performed by hepatobiliary specialists rose from 31.6 to 52.7 per cent, but this was not statistically significant ($P = 0.13$). However, for cholecystectomy in the same period the proportion performed by hepatobiliary surgeons rose from 40.4 to 58.5 per cent, representing a highly significant trend ($P < 0.001$). Following cholecystectomy alone there was a significantly shorter stay associated with patients treated by hepatobiliary surgeons ($P = 0.002$, F test), although the median postoperative hospital stay was 2 days for both groups of surgeons (interquartile range 1–3 days for hepatobiliary and 1–4 days for non-hepatobiliary surgeons).

Conclusions: Although cholecystectomy is not viewed as a specialist procedure, the trend in this teaching hospital reveals a steady increase in the proportion of cholecystectomies being performed by teams with a biliary interest. The data indicate that this practice is associated with a shorter hospital stay.

Investigating the proximal limit of lymphadenectomy in patients with adenocarcinoma of the oesophagus in the mid-thoracic region

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Aims: The benefit of extended lymphadenectomy in patients with squamous cell carcinoma of the oesophagus is established, but there is little evidence to support this in patients with adenocarcinoma. The aim of this study was to investigate the extent of lymphatic spread of oesophageal adenocarcinomas, and particularly the proximal spread in tumours located in the mid thorax.

Methods: Twenty-six consecutive patients with tumours arising between 29 and 35 cm from the incisor teeth underwent three-stage oesophagectomy with two-field lymphadenectomy, including nodes in the recurrent laryngeal chains. The proximal extent was measured by endoscopic ultrasonography and confirmed at operation, with division of the lymph node harvest into anatomical sites according to the Japanese classification of oesophageal cancer.

Results: There were 21 men and five women, with a mean age of 64 (range 42–78) years; seven patients were lymph node negative in both the mediastinal and abdominal fields. Six patients had nodal metastases more than 2 cm above the tumour and all had extensive involvement of other nodes at the level of the tumour or below, with 7, 7, 9, 12, 15 and 18 nodes positive. There were no patients in whom nodes above the tumour contained metastases while those at the level or below were clear.

Conclusions: Dissection of proximal lymph nodes along the recurrent laryngeal nerve chains in patients with adenocarcinoma of the oesophagus is not warranted. Lymphatic spread above the level of the tumour occurs in association with extensive lymph node involvement elsewhere and removal of proximal nodes from difficult locations is not warranted as a means of improving staging or survival.

Need for staging laparoscopy in patients with gastric cancer

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Aims: The aim of preoperative staging in gastric cancer is to correctly identify patients with advanced disease who should not be subjected to surgery and to allow the treatment of those who are admitted for operation to be planned accurately. This study assessed the impact of a policy of selective staging laparoscopy in patients deemed suitable for curative or palliative surgery, to ascertain whether the selective approach increased the frequency of abandoned or unplanned surgical procedures.

Methods: Fifty consecutive patients with gastric or type III gastro-oesophageal junction cancer staged by computed

tomography (CT) alone, in whom surgery was felt to be appropriate for 'cure' or palliative symptom control, were studied. Specific CT, endoscopic and biochemical criteria were applied prospectively to select out a subgroup of 18 patients who also underwent preoperative staging laparoscopy. The overall accuracy of staging and operative outcomes were assessed.

Results: Using this selective approach the resection rate was 98 per cent, although three patients in each group had their planned procedure altered to a less radical (two in each group) or more radical (one in each group) resection ($P=0.23$). Overall, 41 of 50 patients were staged correctly (accuracy 82 (95 per cent confidence interval 69–90) per cent) and 86 per cent of patients underwent the planned surgical procedure. The only abandoned operation occurred in the staging laparoscopy group.

Conclusions: It is possible to plan a patient's operation accurately without the need for a staging laparoscopy in all cases.

Angiographic embolization for major haemorrhage after upper gastrointestinal surgery

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Aims: Severe postoperative haemorrhage after upper gastrointestinal surgery is a serious complication. This study examined the effectiveness of selective mesenteric angiography (SMA) in localizing a bleeding point and the ability of angiographic haemostatic methods to control bleeding.

Methods: The case notes of a consecutive series of nine patients undergoing urgent SMA during 1996–1998 were analysed. Examination of angiography suite records confirmed the accuracy of patient identification. SMA was performed 18 times with 13 embolizations in nine individuals (seven men; median age 54 (27–73) years). Patients underwent the following operations: Whipple pancreaticoduodenectomy (four patients), pancreatic necrosectomy (two), total gastrectomy (one), cholecystectomy (one) and splenectomy (one). The median interval from surgery to haemorrhage was 15 (2–49) days. Six patients presented with haematemesis/melaena and three with bleeding from drains. Seven had evidence of shock (systolic blood pressure less than 100 mmHg, pulse more than 100 per min); the mean preprocedure haemoglobin concentration was 59 g/l. A median of 8 (4–14) units of blood were transfused before embolization and 4 (2–9) units after. Ten initial endoscopies were performed in six patients, seven of which revealed a source of bleeding. Endoscopic haemostasis was attempted in five and achieved temporary control of bleeding in two.

Results: Angiography revealed a discrete bleeding point in 13 of 18 procedures in eight patients. Where a bleeding point was identified, angiographic embolization using 3–8-mm stainless

steel coils (ten) or a combination of coils and gelatin sponge (three) achieved radiological evidence of haemostasis in all cases. Periprocedural complications occurred in one patient with unintentional partial embolization of the right hepatic artery during embolization of an actively bleeding left hepatic artery pseudoaneurysm. Rebleeding occurred in six patients within 48 h. Three rebleeds were successfully managed with repeat SMA and embolization (one patient required a third embolization); the remaining three required surgery. Definitive radiological haemostasis was achieved in six patients. Five of the nine patients died in hospital, two of whom had been successfully embolized.

Conclusions: In this group of patients, endoscopy contributed relatively little to treatment of postoperative haemorrhage. In contrast, SMA identified a bleeding point in eight of nine patients and achieved definitive control of bleeding in six. SMA and embolization appears to have a useful role in patients with this infrequent but potentially lethal complication.

Specialized intestinal metaplasia: analysis of prevalence, risk factors and association with gastro-oesophageal reflux disease

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Aims: There is an increasing awareness that short (less than 3 cm) segments of Barrett's epithelium and macroscopically normal cardia epithelium may harbour specialized intestinal metaplasia (SIM), a premalignant phenotype. This was a

prospective study of both the prevalence of SIM in an unselected population of patients attending for endoscopy, and the association of SIM with symptoms, lifestyle, medication, endoscopic oesophagitis and carditis.

Methods: Two hundred consecutive patients underwent endoscopy. Biopsies taken from just below the squamocolumnar junction were stained for SIM, and were analysed for carditis and *Helicobacter pylori* infection. A detailed questionnaire of symptoms, tobacco consumption and the use of proton pump inhibitors was completed.

Results: Forty-two patients (21 per cent) had SIM, 19 of 126 (15 per cent) in an endoscopically normal oesophagus, 15 of 63 (24 per cent) in a short segment of Barrett's epithelium and eight of 11 in classical Barrett's oesophagus. Comparative analysis between the SIM positive and negative groups with respect to potential risk factors is outlined below.

	SIM positive (n=42)	SIM negative (n=158)	P
'Non-cardiac chest pain'	6 (14)	8 (5)	0.03
Oesophagitis	11 (26)	20 (13)	0.03
'Carditis'	30 (71)	53 (34)	0.0001

Values in parentheses are percentages

Conclusions: SIM is prevalent in patients undergoing endoscopy, does not correlate with symptoms or with *H. pylori* infection, but is significantly associated with endoscopic and pathological markers of gastro-oesophageal reflux.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

The missing mammographic abnormality

Letter 1

Sir

We read with interest the clinical dilemma by Kerin and Monson (*Br J Surg* 1999; 85: 851–2). The scenario of a missed lesion on stereotactic localization biopsy excision depicted by the article is not supported by data on its occurrence. This prompted us to look at our own figures.

Since 1995, of the 198 patients who had a wire localization excision, only two presented with such a problem. In agreement with our findings, audit figures presented at the British Association of Surgical Oncology Breast Speciality meeting (April 1999) show that in the UK between April 1997 and March 1998 only 1.3 per cent (range 0.0–3.5 per cent) of patients requiring image assistance for open biopsy necessitated more than one procedure to locate the lesion¹. This is well below the recommended quality assurance standard of less than 5 per cent². Such results would be difficult to improve on, even using stereotactic automated biopsy equipment. This makes the use of such equipment difficult to justify, particularly as it is expensive and cannot be used for any other procedure.

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1 An audit of screen detected breast cancers for year of screening, April 1997 to March 1998. NHS Breast Screening Programme and British Association of Surgical Oncology, April 1999

2 Quality assurance guidelines for radiologists. NHS BSP Publication no 15, May 1997

Letter 2

Sir

We read with interest the article by Kerin and Monson and entirely agree that significant improvements are required in achieving definitive non-operative diagnosis of screen-detected palpable breast lesions. With modern imaging and percutaneous biopsy techniques it should be possible to achieve a definitive diagnosis in most patients without resort to surgery¹. Exceptions are a diagnosis of radial scar or atypical ductal hyperplasia where a wider surgical biopsy is required to definitively exclude malignancy^{2,3}. We disagree that very wide bore techniques will largely solve this problem. The advanced breast biopsy instrumentation (ABBI) system has been the

subject of mixed reports in recent literature and has a reputation for being a difficult technique with significant complication and failure rates (30 per cent)^{4,5}. This technique also requires expensive prone biopsy table technology. Use of a 14-G hand-held automated needle core biopsy under image guidance should provide a definitive diagnosis in at least 90 per cent of patients⁶. The more flexible technique of image-guided, vacuum-assisted mammotomy, carried out under radiographic or ultrasonographic control, provides operator choice of the amount of tissue removed and provides the diagnosis in the remainder⁷. We caution against any suggestion that needle biopsy techniques can be considered therapeutic for any breast malignancy.

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Authors' reply

Sir

We agree with Zammit *et al.* that every effort should be made to ensure that this clinical dilemma is a rare occurrence and essentially it should not happen. This clinical dilemma, although rare, does occur within the NHS Breast Screening Programme and we attempted to identify ways of solving the problem while giving advice on preventing its occurrence. Wilson *et al.* are correct in stating that improvements in imaging and biopsy techniques should allow a preoperative diagnosis in most patients. Unfortunately, a preoperative diagnosis is achieved in less than 70 per cent of patients. While

this diagnostic rate is probably increasing, frequently more than 20 g of breast tissue is removed to make a benign diagnosis. Techniques such as the ABBI have received mixed reports perhaps because they have been practised in the non-specialist centres and most experience has been obtained outside the setting of a breast screening programme. It is our belief that the concept of excision of image-detected impalpable lesions, such as small cancers or radial scars, using image assistance is wholly reasonable and the way of the future. It seems intuitively sensible that as imaging technology has allowed detection of smaller and smaller lesions that this same technology should be utilized in treatment. We agree that the emphasis must be to minimize the number and invasiveness of interventions to achieve a benign diagnosis. The reality of everyday clinical practice is that a clinical dilemma such as the one described can occur. The challenge is how best to apply complementary techniques such as mammotomy and ABBI in an appropriate and cost-effective manner.

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Local recurrence after curative excision of the rectum for cancer without adjuvant therapy: role of total anatomical dissection

Sir

We read with interest the paper by Bokey *et al.* (*Br J Surg* 1999; 86: 1164–70) and share most of their conclusions but think that there are some points worthy of further consideration. Tumours of the proximal or distal rectum can be treated by different surgical methods. For instance, the comparison between restorative operations and abdominoperineal excisions showed no difference in the 5-year recurrence rate, but the two procedures were applied to tumours in different locations. It would have been interesting to compare low and extended low anterior resections to the abdominoperineal excisions since these procedures were probably performed for tumours of the distal rectum. A recent analysis¹ of tumours located in the low and middle rectum reported a high local recurrence rate after sphincter-saving resection in comparison with the abdominoperineal excision.

Although we agree² about the importance of obtaining a distal margin clearance of 1–2 cm from the tumour, this appears to be much more relevant in restorative operations than in abdominoperineal resection where it does not necessarily imply a high risk for local recurrence. Since tumour spread within the mesorectum usually does not exceed³ 2 cm, this may explain the similar results of partial and total mesorectal excisions. In keeping with this view Zaheer *et al.*⁴ advocate the adoption of a 'tumour-specific' mesorectal excision, recommending it only for tumours located in the low or middle rectum.

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- 1 Bozzetti F, Mariani L, Miceli R, Docì R, Montalto F, Andreola S *et al.* Cancer of the low and middle rectum: local and distant recurrences, and survival in 350 radically resected patients. *J Surg Oncol* 1996; 62: 207–13.
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Author's reply

Sir

We thank Drs Bozzetti and Bertario for their comments. In reply, first, we did in fact compare the local recurrence rate following low and extended low anterior resection and found no difference. Only 18 patients had had a coloanal pull-through and these numbers are too small for meaningful comparison. It is evident from our results (and it makes good sense) that the incidence of local recurrence is primarily related to the pathological characteristics of the tumour rather than the distance of the tumour or subsequent anastomosis from the anal verge.

Second, we agree that distal margins of clearance are only relevant to patients undergoing a restorative procedure.

Third, in this paper we have emphasized that total mesorectal excision should only be performed in patients with a tumour in the middle or lower rectum and we thank Drs Bozzetti and Bertario for concurring with this recommendation.

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Laparoscopy extends the indications for liver resection in patients with cirrhosis

Sir

Abdel-Atty *et al.* (*Br J Surg* 1999; 86: 1397–1400) infer that a successful outcome was only possible using the laparoscopic

approach but relevant points pertaining to open liver resection in patients with severe cirrhosis deserve emphasis. Limited resection, rather than traditional major hepatectomy is appropriate, even in patients with Child's C cirrhosis¹, after a careful assessment of the functional reserve. This reduces morbidity and mortality, with no significant compromise in terms of recurrence or survival².

The use of intraoperative ultrasonography and intermittent hilar clamping³ has markedly reduced the need for blood transfusion even during open procedures⁴. The use of low central venous pressure (less than 4), the argon-beam coagulator and fibrin glue have all contributed to significantly improved results⁴.

In cirrhotic patients in whom a resection is possible, transplantation will give better recurrence² and survival⁵ rates, but limited organ numbers limit its use.

The comment regarding not dividing the ligaments of the liver (possibly contributing to few problems with ascites) was interesting, especially as they found difficulty in resecting one tumour in segment 7, which promptly recurred. Other groups⁶ routinely divide the ligaments to improve access. Why should intractable ascites be a leading cause of postoperative mortality, when in most series it is due to postoperative liver failure⁷, usually precipitated by some surgical complication.

The laparoscopic approach, although exciting, needs to be compared with current open limited resections before attributing these gains to laparoscopy alone.

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Prospective study of primary anastomosis without colonic lavage for patients with an obstructed left colon

Sir

Naraynsingh *et al.* (*Br J Surg* 1999; **86**: 1341–3) are congratulated for the excellent results achieved in the management of patients with left-sided malignant colonic obstruction (mortality and anastomotic leak rates of less than 2 per cent respectively).

Postoperative morbidity and mortality in patients with obstructing colorectal carcinoma is related to preoperative medical condition, cardiovascular stability¹, the presence of bowel perforation, sepsis or metastatic disease^{1–3}, faecal loading⁴ and the type of operation performed³. None of these details was given in this paper. A detail of the timing of surgery (from the time of admission), type of resection (whether segmental colectomy, subtotal colectomy or anterior resection) and the number of patients with an anastomosis below the peritoneal reflection would also be helpful. In the absence of an objective evaluation of the perioperative condition of these patients (Acute Physiology and Chronic Health Evaluation or Physiological and Operative Severity Score for enUmeration of Mortality and morbidity scores) it is difficult to draw conclusions. Were patients with a high risk of anastomotic failure, such as those with peritonitis, bowel perforation, gross debilitation, circulatory instability or immunosuppression, included in the series? Were there any exclusion criteria? What was the Dukes staging of the resected tumours? Were there any patients with synchronous tumours, peritoneal carcinomatosis or advanced metastatic disease? As this was a 9-year prospective follow-up are there any data on median survival? Without these preoperative, perioperative and postoperative data it would probably not be prudent to dispense with a well proven modality (on-table colonic lavage). A randomized controlled prospective trial is required.

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Author's reply

Sir

We agree with Sudhindaran and Sinha that a randomized controlled prospective trial should be performed to examine the outcome of primary resection with and without on-table lavage and this would be best achieved in a centre dealing with a larger number of patients. As indicated in our paper we have been doing on-table lavage previously¹. The obstructed colon usually contains gas, liquid and faecal matter which are easily removed via a 36-Fr tube. On-table lavage washes the colon surface clean of liquid residue rather than eliminating masses of solid faecal matter. There is evidence that complete cleaning of the colon of faecal matter is not necessary for ensuring anastomotic integrity^{2,3}. None of our patients had perforation or synchronous lesions and, although seven had metastases, none had generalized peritoneal carcinomatosis. All patients had segmental resections and although the rectum was mobilized to facilitate resection and anastomosis in two patients the actual site of anastomosis was always above the peritoneal reflection. As indicated in the paper, there were no exclusion criteria and no exclusions. Long-term outcome was not part of this study since it did not seem relevant to the immediate surgical crisis.

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Evaluation of pylorus-preserving pancreatoduodenectomy with the Imanaga reconstruction by hepatobiliary and gastrointestinal dual scintigraphy

Sir

I was interested to read the excellent article by Hishinuma (*Br J Surg* 1999; 86: 1306-11) in which they evaluate the results of the Imanaga reconstruction following pylorus-preserving pancreatoduodenectomy. Having used this technique I have two comments.

As the first step in the gastrointestinal reconstruction they describe bringing the proximal jejunum through the transverse mesocolon. Unless the mesocolon has already been breached during dissection it is possible to use the normal anatomical route for the jejunal loop and clinically this appears to give an equally satisfactory result.

Since the Imanaga reconstruction restores the normal configuration of the upper gastrointestinal tract it is possible to use standard endoscopic stents for the biliary and pancreatic anastomoses. These can be removed endoscopically after a suitable interval following a plain abdominal radiograph in case spontaneous passage has already occurred.

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Author's reply

Sir

We thank Mr Lightwood for his interest in our paper. We do not raise the proximal jejunum via the normal anatomical route behind the superior mesenteric artery (SMA) in pylorus-preserving pancreatoduodenectomy with the Imanaga reconstruction technique (PPPD-Imanaga). In cancer of the pancreatic head, we routinely combine intraoperative radiotherapy (IORT) with PPPD-Imanaga. If the jejunal loop is brought through the normal anatomical route, fibrous adhesions around the SMA caused by IORT might restrict the motility of the jejunal loop. It is also possible that local recurrence around the root of the SMA due to perineural invasion (frequently observed after resection of pancreatic cancer) might provoke obstruction of the jejunal loop. Compression of the jejunal loop by the SMA itself might occur. These concerns led us to use the route through the transverse mesocolon. PPPD-Imanaga enables postoperative endoscopic observation of the status of the anastomoses. To perform such endoscopic observation easily we make the distances between the anastomoses as short as possible. We have had no experience with endoscopic stenting for biliary and pancreatic anastomoses but routinely check the patency of the pancreatic and biliary ducts by endoscopy at different times after surgery. In more than 90 per cent of patients we can identify the orifices of the pancreatic and bile ducts and usually perform retrograde pancreatography and cholangiography. Exocrine function of the remnant pancreas can be evaluated by observing the secretion of pancreatic juice. In one patient who developed pancreatitis endoscopic examination revealed severe stenosis of the orifice of the pancreatic duct and balloon dilation was successfully carried out. Endoscopic examination has revealed local recurrence around the pancreatic and biliary anastomoses in some patients and this reconstruction can therefore be recommended to allow early detection of local recurrence.

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Surgical management of severe secondary peritonitis

Sir

I read with interest the review by Bosscha *et al.* (*Br J Surg* 1999; 86: 1371–7) concerning the surgical management of severe secondary peritonitis in which the authors conclude that aggressive surgical strategies may have reached their limits. Scheduled reoperation is of proven efficacy in significantly reducing mortality rates especially in patients in whom the source of infection cannot be controlled at the initial operation. It also led to high postoperative morbidity^{1,2}. Relaparotomy after initial eradication of the source of infection has demonstrated the efficacy of surgical re-exploration within 48 h of the initial operation^{3–7}. Worse results of relaparotomy on demand can be explained by delayed performance reoperation^{5–8}, but this protocol implies a higher rate of unnecessary reoperation.

Some patients are prone to persisting abdominal infection regardless of initial surgical cleansing and eradication of the source of infection. Such patients are often elderly, frail and immunologically impaired. These factors contribute to an anergic state and an adverse outcome even after successful surgical and intensive care treatment. The overwhelming cytokine-mediated inflammatory response to infection may lead to multiple organ dysfunction syndrome and death^{8–11}.

The future challenge is to better define patients who would benefit from aggressive surgical strategies at the initial operation, regardless of the futility of carrying out prospective randomized studies in reoperative surgery in patients with secondary peritonitis.

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Author's reply

Sir

We thank Dr Koperna for his interest in our paper and agree that the worst results of relaparotomy on demand can be explained by the delay¹. Although planned relaparotomies can lead to a higher rate of unnecessary reoperation, they are of proven benefit in patients in whom the source of infection cannot be totally controlled at the initial operation. Open management of the abdomen should be reserved for patients needing more than two reoperations and for those in whom closure of the abdominal wall is impossible^{2,3}.

The question regarding a better definition of patients who would benefit from aggressive surgical treatment strategies is of much interest. It can only be settled, however, by well documented prospective randomized trials, including a detailed description of patients and the severity of their disease. Further studies are necessary to select high-risk patients for repeat surgery because poor prognosis may even justify decisions not to start treatment. Recently, we showed that patients with a combination of an Acute Physiology and Chronic Health Evaluation II score of 20 or more and a Mannheim Peritonitis Index of 27 or greater seem to be in such a desperate position. If other studies confirm these findings then aggressive surgical treatment strategies should not be started in these patients at all⁴.

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- 1 Hau T, Ohmann C, Wolmershäuser H, Wacha H, Yang Q. Planned relaparotomy *versus* relaparotomy on demand in the treatment of intra-abdominal infections. The Peritonitis Study. *Arch Surg* 1995; 130: 1193–7.
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Randomized controlled trial to examine the influence of thoracic epidural analgesia on postoperative ileus after laparoscopic sigmoid resection

Sir

Recently, Neudecker *et al.* (*Br J Surg* 1999; 86: 1292–5) concluded that perioperative thoracic epidural analgesia did not have a clinically relevant effect on ileus after laparoscopic colonic resection. I have some observations on this study.

First, they used a low thoracic (T9–12) epidural, which may explain the side-effects and the lack of a positive effect on ileus since a higher thoracic segmental blockade is needed^{1–3}. This explains the positive results in previous randomized trials.

Second, the non-significant reduction in duration of paralytic ileus (54 versus 77 h) in such a small study may not allow a 'clinical' conclusion due to the risk of a type II error. Future trials to document the effects of epidural analgesia on postoperative ileus should, therefore, be of sufficient size and use an appropriate level of thoracic epidural analgesia and multimodal rehabilitation^{2,3} to achieve clinically relevant conclusions.

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- 1 Steinbrook RA. Epidural anesthesia and gastrointestinal motility. *Anesth Analg* 1998; 86: 837–44.
- 2 Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. *Lancet* 1995; 345: 763–4.
- 3 Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation program. *Br J Surg* 1999; 86: 227–30.

Authors' reply

Sir

We thank Dr Kehlet for his interest in our study. We attempted to reproduce the results of Bardram *et al.*¹ in whose study a 'thoracic epidural catheter was inserted between T7 and T9', whereas our catheters were between T9 and T12. Regular postoperative skin prick testing ensured that the level of regional blockade reached T4/T5 in every patient. The sample size was calculated according to the results of Bardram *et al.*¹ (experimental group: thoracic epidural analgesia, 30 h) and from a previous prospective randomized trial² (control group: no thoracic epidural analgesia, 70 h). The sample size in our study was sufficient to detect the differences with a two-sided test and $\alpha = 0.05$ and $\beta = 0.2$. A smaller difference may not have been detected in our trial but a smaller advantage in the epidural group would not justify the additional effort required by thoracic epidural analgesia.

On the basis of the data available, thoracic epidural analgesia using local anaesthetic may be indicated to shorten post-

operative ileus in patients undergoing conventional colorectal resection but cannot be recommended as a standard technique to shorten postoperative ileus in patients undergoing laparoscopic surgery. We do agree with Dr Kehlet that multimodal rehabilitation, including thoracic epidural analgesia, is an interesting way of improving the postoperative course. The promising results of small uncontrolled studies^{1,3} are still awaiting confirmation by prospective randomized trials.

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- 1 Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. *Lancet* 1995; 345: 763–4.
- 2 Schwenk W, Böhm B, Haase O, Junghans T, Müller JM. Laparoscopic versus conventional colorectal resections: a prospective randomised study of postoperative ileus and early postoperative feeding. *Langenbecks Arch Surg* 1998; 383: 49–55.
- 3 Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. *Br J Surg* 1999; 86: 227–30.

Emerging trends in the management of the impalpable testis

Sir

I refer to the recent paper by Flett *et al.* (*Br J Surg* 1999; 86: 1280–3) and agree that examination under anaesthesia is important before surgical intervention. I still prefer the Fowler–Stephens approach¹, however, and strongly refute the remark that retroperitoneal exploration is often undertaken incorrectly by 'adult' surgeons who have not had appropriate paediatric training.

The impalpable abdominal testis is an intraperitoneal organ amenable to recognition and management by laparoscopy or a microlaparotomy via an iliac fossa incision.

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- 1 Ahmed S, Mallick S, Fouda-Neel K. Fowler–Stephens orchidopexy revisited. *Urol News* 1999; 3: 6–8.

High early mortality rate from acute pancreatitis in Scotland, 1984–95

Sir

In this paper (*Br J Surg* 1999; 86: 1302–6) studying disease patterns in patients with acute pancreatitis in

Scotland the authors conclude that there is an urgent need for early recognition of those with severe disease to facilitate transfer to centres with 'high-dependency and intensive care facilities supervised by a multidisciplinary team'. They infer that early mortality may be reduced by such a policy but provide no information to sustain such a conclusion.

De Beaux *et al.*¹ suggested that delay to referral influenced outcome but a more recent analysis of the same Edinburgh data (but over a longer time period) found no correlation between disease outcome and delay to referral². Validation of the authors' statement requires a prospective analysis of outcome in patients admitted *de novo* to district general and university hospitals. If such an analysis were to demonstrate differences in survival there would be a case for early transfer, but this change is complicated by the trend towards increasing subspecialization in general surgery. Many large district hospitals will have clinicians working in teams with a declared upper gastrointestinal interest. In this context the recent Association of Upper Gastrointestinal Surgeons manpower document indicates that treatment of acute pancreatitis may remain a core activity (personal communication).

While it is tempting to state that all patients with severe acute pancreatitis should be transferred to specialist units there is a need for objective evidence that such a policy would improve disease outcome.

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1 De Beaux AC, Palmer KR, Carter DC. Factors influencing morbidity and mortality in acute pancreatitis, an analysis of 279 cases *Gut* 1995; 37: 121–6.

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Endoscopic totally extraperitoneal repair of bilateral inguinal hernias

Sir

We read with interest the recent article by Knook *et al.* (*Br J Surg* 1999; 86: 1312–16) and agree that laparoscopic hernia repair should be considered in the treatment of all bilateral inguinal hernias. We would appreciate clarification of two points.

First, we are not familiar with the intraoperative findings during the treatment of recurrent hernia. The authors have performed five transabdominal preperitoneal (TAPP) procedures for recurrence. What was the appearance of the peritoneal wall? Were there any intra-abdominal adhesions? How did they dissect the preperitoneal space?

Second, while performing the TAPP procedure we fasten the sheet of mesh on either side of the cord by staplers to prevent mesh migration¹. Instead of using a single large prosthesis for the prevention of recurrence, securing the mesh to both Cooper's ligament and abdominal wall would be more appropriate. As the authors did not secure the prosthesis, could this be the cause of recurrence?

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1 Swanstrom LL. Laparoscopic herniorrhaphy. *Surg Clin North Am* 1996; 76: 483–91.

Glenn's Urologic Surgery. 5th ed.

S. D. Graham Jr (ed.)

287 × 224 mm Pp. 1149 Illustrated 1998 Philadelphia, Pennsylvania: Lippincott Williams and Wilkins \$195

This textbook, now in its fifth edition, was first published in 1969. It gains its title from the premise that, as stated in the preface to the first edition, 'Urologists are – first and foremost – surgeons'. There are 16 editors and 187 contributing authors, many of whom are established experts in their field, although (as is the trend with most current textbooks) the majority of these are from the USA. In keeping with a change in editors, the layout of this edition has been changed and is now based on division into 14 different sections rather than by chapter. It is unfortunate that the new editors did not use the opportunity of a change in style to improve the size and clarity of the diagrams. These are still small, often unclear, and are even duplicated in different areas of the book. There are notable exceptions: the section on perineal prostatectomy is an excellent example of clear illustrations. The work is a combination of a textbook of urology and a surgical atlas. As such it occasionally tries to cover too many areas but, on the whole, it is a reasonable reference text for a urological trainee to use. However, it has no clear advantages over other currently available operative texts.

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Applied Radiological Anatomy

P. Butler, A. W. M. Mitchell and H. Ellis (eds)

282 × 224 mm Pp 441. Illustrated 1999. Cambridge Cambridge University Press. £110

The use of radiological imaging to teach anatomy makes for a happy marriage between basic science and clinical medicine; the editors are to be congratulated in achieving this. There can also be no better means of demonstrating the increasing subspecialization in radiology than by review of these chapters. Although no more than a basic overview of imaging methods, the examples used are excellent to fulfil the function of the book as an anatomy primer for Part I of the FRCR Diploma. The two chapters written by Harold Ellis should be compulsory reading for all trainee radiologists and surgeons. As in any multiauthor book, the chapter layout varies, but generally follows the pattern of an overview of available radiological methods, followed by an illustrated anatomical description with relevant radiological images. This works well but in some areas monochrome line drawings alone have been used with less success, particularly in large complex areas such as a coronal section through the male pelvis. There is also considerable variation among chapters in the details of different imaging

methods and their complications, particularly for those that are invasive. There are some omissions; nerve damage is referred to as a complication of femoral and brachial artery cannulation but intimal dissection and false aneurysm are not. There are also some errors, for example, the urachus is said to form the median umbilical ligament and the femoral artery is described as entering the thigh at the mid inguinal point 'halfway between the anterior superior inguinal spine and the pubic tubercle'. There are also a small number of typographical errors. These points aside, this book is first class in achieving its aim and, although primarily intended for trainees in radiology, will be of value to many surgical trainees.

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The Art of Surgery. Exceptional Cases – Unique Solutions. 100 Case Studies

M. Trede

305 × 234 mm Pp 212 Illustrated 1999 Stuttgart Georg Thieme DM 248

In these days of information plethora, multiauthor volumes about surgical diseases abound in all specialties. The writing standard on which most of these books are built is the systematic review of a given topic, supported by scientific analysis of large series of patients. Few books, however, deal with the unusual cases that challenge the craft and the imagination of the surgeon and help him, through life, to build his or her personal know-how. This text is one such book. It consists of 100 magnificent surgical sketches, illustrating technically complex gastrointestinal surgery cases, 40 of them dealing with the pancreas, drawn by the author himself. The sequential drawings of difficult operations (superbly reproduced by Thieme) are accompanied by a short summary of each case (including imaging, and pathological and operative photographs) and a 'lesson'. Some of these lessons challenge current surgical dogmas while others, written with the perspective of time, reflect positive criticism which, as we learned from Karl Popper, is essential for the acquisition of new knowledge. Surgeons will find in this book unique graphic descriptions of unusual cases, postoperative complications and surgical techniques used in their management. The surgeon specialized in pancreatic surgery will particularly enjoy visiting this outstanding drawing exhibit, gathered by an outstanding artist and master of surgery.

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Scientific Surgery

Kortbeek JB, Haigh PI, Doig C. Duodenal *versus* gastric feeding in ventilated blunt trauma patients: a randomised controlled trial. *J Trauma* 1999; 46: 992–6.

The study included 80 patients, feeding started within 72 h of injury. Transpyloric duodenal feeding appeared to reduce the rate of pneumonia (27 *versus* 42 per cent, *P* not significant), but not the duration of intensive care or hospital stay.

Kald A, Kullman E, Anderberg B, Wiren M, Carlsson P, Ringqvist I *et al.* Cost minimization analysis of laparoscopic and open appendicectomy. *Eur J Surg* 1999; 165: 579–82.

The trial included 102 patients, all who recovered fully within 2 months. The mean duration of hospital stay, time off work and time to complete recovery were similar. The only difference was that laparoscopic appendicectomy incurred higher direct costs.

Fynes MM, Marshall K, Cassidy M, Behan M, Walsh D,

O'Connell PR *et al.* A prospective randomised study comparing the effect of augmented biofeedback with sensory biofeedback alone on fecal incontinence after obstetric trauma. *Dis Colon Rectum* 1999; 42: 753–7.

Forty women with incontinence after obstetric anal sphincter damage were evaluated. Continence scores and anal squeeze pressures were improved in patients who had augmented biofeedback.

Pinto A, Fidalgo P, Cravo M, Midoes J, Chaves P, Rosa J *et al.* Short chain fatty acids are effective in short-term treatment of chronic radiation proctitis: a randomized double blind controlled trial. *Dis Colon Rectum* 1999; 42: 788–94.

In this study of 19 patients, short chain fatty acid enemas for 5 weeks were compared with placebo. At 5 weeks, actively treated patients had less rectal bleeding, higher haemoglobin levels and improved endoscopic scores. By 6 months both groups were similar as placebo patients gradually improved spontaneously.

Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA *et al.* The effect of raloxifene on the risk of breast cancer in postmenopausal women: results from the MORE randomised trial. *JAMA* 1999; 281: 2189–97.

Some 7705 women with osteoporosis taking either raloxifene or placebo were monitored. The incidence of breast cancer in treated patients was reduced significantly (relative risk 0.24, 95 per cent confidence interval 0.13–0.44, *P* < 0.001).

Rautalahti MT, Virtamo JR, Taylor PR, Heinonen OP, Albanes D, Haukka JK *et al.* The effects of supplementation with alpha-tocopherol and beta-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized controlled trial. *Cancer* 1999; 86: 37–42.

Some 29133 men aged 50–69 years were randomly allocated dietary supplementation or placebo. After 5–8 years there was no statistically significant effect on either the incidence or the mortality rate from pancreas cancer.

O'Hea BJ, Ho MN, Petrek JA. External compression dressing *versus* standard dressing after axillary lymphadenectomy. *Am J Surg* 1999; 177: 450–3.

Some 135 patients were randomized to a compression dressing for 4 days in addition to suction drains, or a control group. Compression did not reduce the drainage volume, days that drainage was required or the seroma rate.

Elliott CG, Dudney TM, Egger M, Orme JF, Clemmer TP, Horn SD *et al.* Calf-thigh sequential pneumatic compression compared with plantar venous pneumatic compression to prevent deep vein thrombosis after non-lower extremity trauma. *J Trauma* 1999; 47: 25–32.

Venous duplex imaging was used to assess the deep venous thrombosis (DVT) rate after 8 days in this study of 149 patients. The rate was significantly less after calf-thigh compression (6.5 *versus* 21 per cent, *P* = 0.009). Seven of 13 affected patients in the plantar compression group had a bilateral DVT.

Higgins A, London J, Charland S, Ratzer E, Clark J, Haun W *et al.* Prophylactic antibiotics for elective laparoscopic cholecystectomy: are they necessary? *Arch Surg* 1999; 134: 611–14.

This study included 450 patients allocated into three equal groups – a single intravenous injection of cefotetan, cephazolin or placebo. The ten postoperative infections were equally distributed within the groups and no advantage for routine antibiotic prophylaxis was demonstrated.

Jackson MR, Gillespie DL, Longenecker EG, Goff JM, Fiala LA, O'Donnell SD *et al.* Hemostatic efficacy of fibrin sealant (human) on expanded polytetrafluoroethylene carotid patch angioplasty: a randomized clinical trial. *J Vasc Surg* 1999; 30: 461–7.

Forty-seven patients were randomized to receive fibrin sealant or a thrombin soaked gelatin sponge after patch angioplasty. Time to haemostasis and measured blood loss were similar.

Tangelder MJD, Lawson JA, Algra A, Eikelboom BC. Systematic review of randomized controlled trials of aspirin and oral anticoagulants in the prevention of graft occlusion and ischemic events after infrainguinal bypass surgery. *J Vasc Surg* 1999; 30: 701–9.

All interventions reduced the rate of graft occlusion. Antiplatelet therapy (five studies), relative risk 0.78, 95 per cent confidence interval 0.64–0.95, anticoagulants (one study) 0.55, 0.3–0.99; combination (one trial) 0.38, 0.15–0.95.

Marroni M, Cao P, Fiorio M, Maghini M, Lenti M, Repetto A *et al.* Prospective randomized double blind trial comparing teicoplanin and cefazolin as antibiotic prophylaxis in prosthetic vascular surgery. *Eur J Clin Microbiol Infect Dis* 1999; 18: 175–8.

Single dose intravenous prophylaxis was randomly allocated in 238 patients. Clinical outcomes (wound and graft infection rate, and mortality) were similar, but teicoplanin treatment was more expensive.

Instructions to authors

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Abstract

This must not exceed 200 words and should be presented in a structured format. **Background:** state why the study was done and its main aim. **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings including important numerical values. **Conclusion:** state the main conclusions but controversial or unexpected observations may be highlighted.

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Use abbreviations *sparsingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension.

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For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; 78: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

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Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637–9).

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Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values

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Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

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Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript.¹ or ^{1–3}. References cited only in tables or figures should be numbered in sequence.

Occult insulinoma

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Insulinoma is a rare neuroendocrine tumour with an incidence of approximately four per 5 million of population¹. Most of the time it is easy to diagnose, localize and remove, allowing complete alleviation of the dramatic, and sometimes life-threatening, symptoms of neuroglycopenia. Sometimes, however, this may not be so; despite adequate knowledge of its size and location, an insulinoma may be occult and difficult to localize both before and during surgery. Medical therapy, in the form of diet modification plus diazoxide or verapamil, can control hypoglycaemic symptoms in approximately 60 per cent of patients with insulinoma, but operation remains the only curative treatment. The urgency of surgery is related to the severity of symptoms and the ability to manage them medically. In general, if hypoglycaemia can be managed medically, there is less immediate pressure on the surgeon to find and remove the tumour. However, if symptoms are poorly controlled with medical management, the operation must be successful.

Insulinoma, first recognized by Whipple in the 1930s², is the most common pancreatic islet cell tumour and is malignant in only 5–11 per cent of cases. In its sporadic form (90 per cent) tumours are generally solitary, whereas in its familial form (10 per cent), they are multiple, especially in the setting of the multiple endocrine neoplasia (MEN) type 1 syndrome. Although insulinoma may occur throughout life, the mean age at presentation is 45 years and the female to male ratio is just under 2 : 1. Approximately 80–90 per cent of insulinomas are less than 2 cm in size and the lesions are distributed equally throughout the head, body and tail of the pancreas. Approximately 5–10 per cent of insulinomas occur as multiple tumours associated with MEN-1¹. The presence of diffuse microadenomatosis, in which multiple small non-encapsulated tumours or nodules are distributed throughout the pancreas (nesidioblastosis), may occur in the neonatal and infant setting and cause hypoglycaemia. This entity, however, is largely absent in adults.

Almost all patients with insulinoma have symptoms due to hypoglycaemia. Most commonly these are neuroglycopenic in nature, including seizures, difficulty awakening, visual disturbance, confusion, lethargy, weakness and transient motor deficits. Hypoglycaemia also results in catecholamine release with subsequent sympathetic dis-

charge causing sweating, anxiety and palpitations¹. Erroneous psychiatric or neurological diagnoses are common in such situations and, on average, it takes up to 2 years before the correct diagnosis is made³. Whipple originally proposed the diagnostic triad of symptomatic hypoglycaemia induced by fasting, a blood glucose level below 2.48 mmol/l (45 mg/dl), and prompt relief of symptoms following administration of glucose². Since that time, the development of a sensitive radioimmunoassay for insulin has simplified the diagnosis of insulinoma. The diagnostic test of choice is a fast during which serum levels of glucose and insulin are measured at 6-h intervals. The fast is terminated at 72 h or when the patient develops neuroglycopenic symptoms; most patients with insulinoma develop symptoms within 12–24 h and none will be able to fast for 72 h. Administration of the test requires hospitalization to monitor symptoms, draw blood and exclude the use of either insulin or oral hypoglycaemic drugs which produce factitious hypoglycaemia, a state that may closely mimic insulinoma. When neuroglycopenic symptoms develop, a serum glucose level less than 2.48 mmol/l (45 mg/dl) and concomitant insulin level greater than 5 units/ml establish the diagnosis.

A large variety of imaging modalities have been used to localize insulinomas before operation. Overall, no single study has been able to perform this task with a high level of specificity. Computed tomography (CT), magnetic resonance imaging and ultrasonography identify only 17–26 per cent of tumours⁴. CT is indicated in order to exclude liver metastases or the presence of a large malignant primary tumour. Somatostatin receptor scintigraphy is also poor at imaging insulinomas since these tumours do not have a high density of type 2 somatostatin receptors⁵. Because of the inability of preoperative studies to localize an insulinoma accurately, some have recommended surgical exploration with intraoperative ultrasonography, thereby avoiding other costly invasive preoperative imaging techniques. However, it is our opinion that invasive studies may be of some use. Endoscopic ultrasonography appears to be emerging as one of the best preoperative studies to identify insulinoma (*Fig. 1*). However, it requires considerable specialized expertise, is observer dependent and is not available in all centres. It has a sensitivity of 80–85 per cent

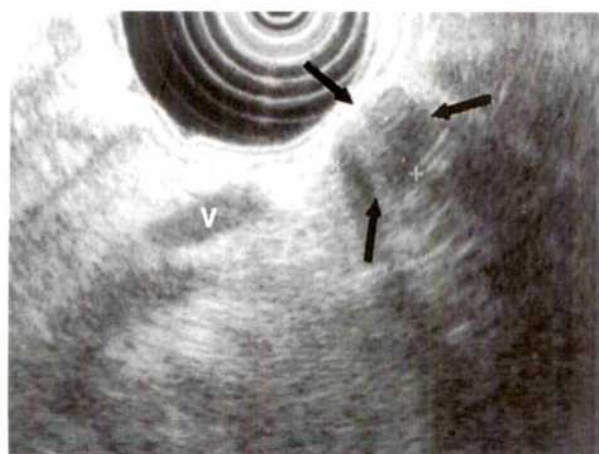


Fig. 1 Endoscopic ultrasonographic appearance of an intrapancreatic insulinoma (arrows). V denotes the portal vein

and a specificity of 95 per cent for identifying intrapancreatic insulinomas⁶. Portal venous sampling for insulin is an older invasive procedure that can locate the region of the pancreas containing the tumour in 75 per cent of patients. It has some disadvantages that include the need for radiological expertise, as well as cost, pain and other complications. Intra-arterial provocative angiography, which has largely supplanted portal venous sampling, provides similar localization information (*Fig. 2*) at less cost and with fewer complications⁷; 90 per cent of insulinomas can be localized correctly with few false-positive results. The most effective method for localizing an insulinoma at surgery is intraoperative ultrasonography⁸, which identifies tumours based on a difference in echogenicity between the lesion and the surrounding pancreas. The insulinoma is seen as a sonolucent and discrete mass (*Fig. 3*). This modality detects approximately 90 per cent of insulinomas and is especially useful for tumours in the thicker pancreatic head.

Despite all efforts, including the use of intraoperative ultrasonography, an occult insulinoma may still be encountered. In the past, different strategies have been used to deal with this problem. Blind distal pancreatectomy, progressive pancreatectomy and subtotal pancreatectomy with intraoperative glucose monitoring have hitherto been recommended. Blind distal and progressive pancreatectomy are no longer indicated, since recent studies indicate that occult tumours are more commonly located within the pancreatic head^{8,9}. Still, it is difficult to advocate performing a Whipple procedure on the basis of circumstantial evidence that the tumour may be present in the pancreatic head. If the tumour is not identified despite a careful exploration with intraoperative ultrasonography, termination of the operation without blind resection is recommended. A repeat 72-h fast may be necessary to be certain of the diagnosis. A trial of

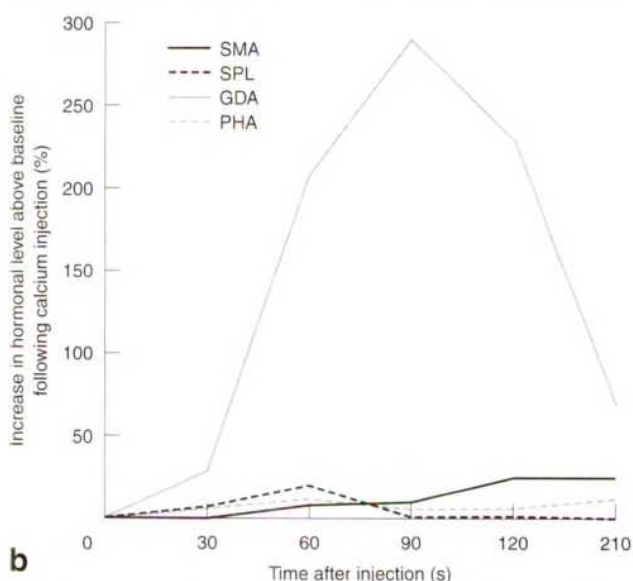
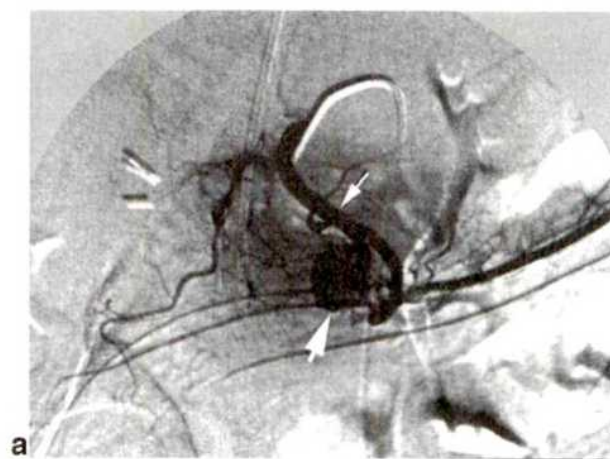


Fig. 2 Provocative angiography identifying an insulinoma in the head of the pancreas.

a A standard arteriogram shows a 2-cm hypervascular blush (large arrow) after injection of the gastroduodenal artery (small arrow).

b The same patient shows a significant increase in insulin sampled from the hepatic vein 90 s after calcium is injected into the gastroduodenal artery (GDA) during the study shown in **a**. Sampling after selective injection of the superior mesenteric artery (SMA), splenic artery (SPL) or proper hepatic artery (PHA) shows no significant increase in hepatic vein insulin levels

the best current medical therapy to stabilize the patient on a short-term basis allows time for calcium angiography, a technique that is useful in localizing the region of the pancreas containing the tumour (*Fig. 2*). At re-exploration, if still no tumour is identified, the area of the pancreas suggested by the calcium angiogram should be removed. One might call this an 'enlightened' resection rather than a 'blind' resection (as advocated previously). However, it

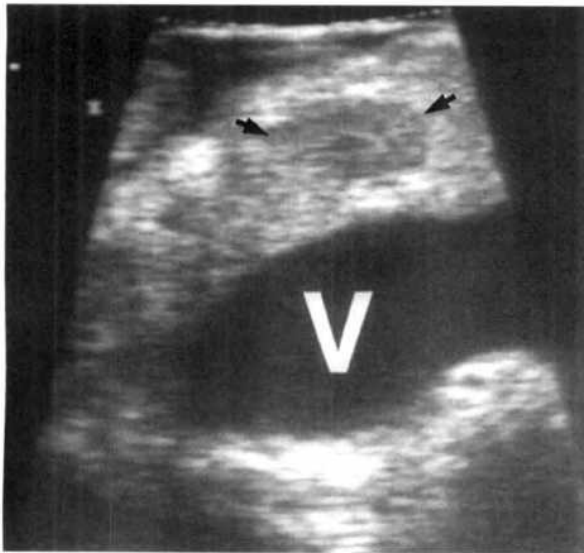


Fig. 3 Identification of an insuloma using intraoperative ultrasonography (arrows). Note the difference in echogenicity between the tumour and surrounding pancreatic tissue. V, portal vein

should be noted that in our experience over 90 per cent of occult insulinomas are identified with intraoperative ultrasonography, thereby eliminating the need for resection based solely on regional localization.

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Generating an idea: will it be publishable?

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Many aspiring surgical authors question whether their plan (or idea) to write about a certain topic of personal interest will be publishable. Ideas are plentiful, but formulating an idea worthy of publication and bringing it to fruition can be difficult. This short discussion addresses the process of generating a potentially 'publishable' idea and provides an outline of relevant and acceptable approaches (not just ideas!). The young or 'naive' author should not be discouraged from 'writing up' a project but rather should use the following guidelines to help focus the development of ideas and realistically define publishable concepts. Each type of submission (Table 1) should fulfil certain basic criteria.

Review articles

This type of publication is especially amenable to the young surgeon without personal clinical experience. These articles require a great deal of library research, however, and the prospective author should begin by asking several pertinent questions. Is there a 'gap' that the planned review will fill? If the topic has not been covered in recent major texts and journals, there is a gap. Other important questions must be addressed. Is the topic of broad enough interest to capture the reader (and the editor)? Are there ongoing but as yet unanswered controversies? Has a recent but not well appreciated consensus been attained? Will this article be primarily of educational benefit alone? For many state-of-the-art journals, the latter is of much less interest and may not attract support.

Case reports

These articles are often the most difficult to justify and get published. While a 'weirdo neoplasm' or a disease process that is 'really interesting' or 'I've never seen one before' might indeed fascinate the prospective author, such a topic is not of itself always of interest for publication. Be careful of claiming 'the first reported case' because, even if true, this fact in itself does not always warrant publication. A case report should be novel, unique or timely, and of sufficiently broad interest to capture a large segment of the readership. Simple archiving of a new but uninteresting or clinically

unimportant process may not be sufficient justification for publication.

Technique paper

The key concepts with this type of submission must involve a unique, novel or new technique, not just 'the master's technique' at a particular university or medical school. Technique papers require a topic of reasonably broad interest and require adequate clinical experience (i.e. number of patients) with appropriate follow-up.

Cohort study and case series

Such articles probably represent the largest category of the surgical literature. Writing up a 'series' on the treatment of a particular disease necessitates a focused, well defined problem with adequate numbers, follow-up and measurable

Table 1 Generating a publishable idea

Type of submission	Key concepts
Review articles	Broad interest, controversy, recent consensus, education
Case report	Novel, unique, timely, broad interest, educational, not necessarily the 'first reported case'
Technique paper	New, novel, broad interest, adequate experience and follow-up
Cohort study and case series	Focused, adequate numbers, well defined problem, available outcome measures, aim and hypothesis
Meta-analysis	Methodology and evaluable published studies are the key
Prospective study	
Randomized	Statistical validity and adequate design, ?blinded
Non-randomized	Established or well accepted controls, relevant interest
Research paper	Hypothesis-driven, mechanistic (<i>versus</i> phenomenological), state-of-the-art, translational, clinical or basic science
Editorial	Solicited <i>versus</i> unsolicited, reputation
Letter to the editor	Broad interest, non-parochial, correction of important error

outcome criteria (e.g. morbidity, mortality, quality of life). Including an aim and hypothesis based on previous work markedly strengthens such a submission. Such articles are more attractive if they offer a new approach rather than just a cataloguing of one's own clinical experience.

Meta-analysis

An appropriate meta-analysis requires the existence of an adequate number of previous reports that fulfil the criteria needed for inclusion in a meta-analysis, such as appropriate patient categorization and clearly definable outcome measures. The key to the publishable meta-analysis is proof of the validity of its methodology; not all 'unanswered' topics are appropriate for such analysis. Close cooperation with a statistician experienced in performing meta-analyses *before* beginning the project is essential.

Prospective clinical study

There are two forms of prospective study: randomized and non-randomized. The buzzword term 'prospective' alone does not guarantee publication.

Randomized studies will be judged based on their statistical validity and design. Are there enough patients realistically to answer the question and hypothesis? Are the evaluators (and/or patients) blinded, especially for subjective outcome measures? These studies should be hypothesis driven with clearly outlined power statements developed *before* initiating the study. *Post hoc* analyses will always be questioned. The best advice is to include the help of a reputable statistician in the study design before starting the study. There is little question that prospective randomized studies represent the 'gold standard' when addressing a testable hypothesis, but when poorly designed or not statistically sound such studies are of little or no value.

Non-randomized studies require a clinically relevant topic with at the least an established clinical outcome or a well accepted control group. When the expected outcome of the 'control' treatment against which the prospective (non-randomized) study is designed to challenge is unknown, the importance offered by such a 'prospective' study may not be able to be evaluated and thus will be of little interest for publication.

Research paper

These articles, ironically, may be the easiest to publish in a more clinically oriented journal, especially if the techniques used involve the 'new' molecular biology. The best approach to developing an idea in the laboratory is to explore a hypothesis-driven question, especially one that addresses the mechanism(s) of a disease or physiological process – not just a phenomenological approach of determining what happens after you perform a particular intervention. These ideas are best developed using state-of-the-art laboratory techniques in a direct translational approach.

Editorials

Most editorials are solicited by the journal from the author. Unsolicited editorials submitted independently usually are not well accepted unless the author is an established authority. Although everyone is entitled to their own opinion, getting your 'opinion' published as an unsolicited editorial may be next to impossible.

Letters to the editor

In contrast to unsolicited editorials, letters to the editor are more readily accepted for publication, especially when the author can identify errors of interpretation or can contrast a different clinical experience not discussed in the original article. The letters should be of broad interest and non-parochial.

Summary

This advice is not intended to discourage the prospective surgical author but rather to provide guidelines and criteria to prevent the inevitable discouragement of a negative review. Many submissions are doomed from the start because of either poor planning or naivety, and both are avoidable. Probably the best advice for the new author is to obtain the opinion of a seasoned author, perhaps not before beginning to research and develop an idea, but certainly before committing too much time and effort into collecting data and writing a manuscript for potential submission. Good ideas that are well developed are published – bad ideas are rejected.

Committee on Publication Ethics

GUIDELINES ON GOOD PUBLICATION PRACTICE

4 Conflicts of interest

Definition

Conflicts of interest comprise those which may not be fully apparent and which may influence the judgement of author, reviewers, and editors.

They have been described as those which, when revealed later, would make a reasonable reader feel misled or deceived.

They may be personal, commercial, political, academic or financial.

Other sections of these guidelines will appear in future issues. The full guidelines are available at www.publicationethics.org.uk.

'Financial' interests may include employment, research funding, stock or share ownership, payment for lectures or travel, consultancies and company support for staff.

Action

- 1 Such interests, where relevant, must be declared to editors by researchers, authors, and reviewers.
- 2 Editors should also disclose relevant conflicts of interest to their readers. If in doubt, disclose. Sometimes editors may need to withdraw from the review and selection process for the relevant submission.

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British Journal of Surgery Referee Trial

In 1998, the Editorial Team conducted a randomized trial to compare whether referees chosen by the authors of manuscripts submitted to the *BJS* gave reports as good as those chosen by the *BJS* editors in the usual manner. The results of the trial were subjected to formal peer review and are published this month in the *Annals of the Royal College of Surgeons of England*. Those who do not receive the *Annals* can read the article by accessing the Journal part of the College website (rcseng.ac.uk).

The study concluded that our authors tended to select referees from the same pool of clinicians as the editors, perhaps not surprising in view of the relatively small surgical community in the UK. There were no major differences between the reports produced by either group of referees, though the editors' referees were slightly quicker and marked a little more harshly. The Editorial Team reviewed the results in detail but found nothing to support a change in current practice. We remain open to suggestions and will consider possible future trials.

BJS referees may not have been aware of the trial and for obvious reasons had to be blinded to the investigation. The editors are conscious of the extra burden this study may have placed on referees and wish to record our sincere appreciation for past and continued support and service to the Journal. We are always ready to hear from our referees with advice on our methods of working, with details of areas of special interest, with names of others who may wish to enjoy the process and with advice on the volume of work that referees can successfully manage.

J.J. Earnshaw
on behalf of the Editorial Team

An unexpectedly normal-looking adrenal gland

A patient has biochemical evidence of Conn's syndrome. Magnetic resonance imaging suggests a left-sided adrenal lesion but on laparoscopic exploration the gland looks normal. How should one proceed? Jean-François Henry of Marseilles, France replies.

In this situation the surgeon should try to answer four questions. First, is it really the adrenal gland that I am exploring? Second, if so, is this gland really normal? Third, if so, how can the magnetic resonance image and the biochemical syndrome be explained? Fourth, what should I do?

Is it really the adrenal gland?

Identification of the left adrenal gland when it is deeply embedded in surrounding fat is sometimes difficult. This explains why several surgeons have mistakenly dissected adjacent structures. Consequently, it must be kept in mind that the tail of the pancreas may be mistaken for a normal left adrenal gland. To avoid this pitfall, dissection of the adrenal gland should start on its medial edge and proceed from its superior to its inferior pole, as deeply as possible, very close to the posterior muscular plane. During this dissection the accessory adrenal vein, which joins the diaphragmatic vein and the main adrenal vein, is often encountered. This accessory vein simply has to be followed in a downward direction, along the medial edge of the gland, to find the main vein and the inferior pole of the adrenal¹.

Is the adrenal gland really normal?

Conn's adenomas are usually small lesions of less than 2 cm in diameter, sometimes even less than 1 cm. When such an adenoma arises posteriorly in the adrenal, the gland may look normal at initial exploration. In these circumstances laparoscopic ultrasonography may be very useful in confirming the presence of a lump in the gland². If laparoscopic ultrasonography is not available, the surgeon must dissect the gland further in order to explore it more completely, particularly its posterior aspect. However, this manoeuvre must not compromise viability and so dissection of the inferior pole of the gland is not recommended. The surgeon must dissect at the superior pole and the lateral edge, very close to the kidney, sufficiently to enable rotation of the gland on itself without any damage to the main adrenal vein.

How can the magnetic resonance image and biochemical syndrome be explained?

If the adrenal looks normal after detailed laparoscopic exploration, the magnetic resonance image should be questioned. Although magnetic resonance imaging (MRI) is used because of its ability to reveal tissue-specific characteristics, it can sometimes falsely present other space-occupying tumours as adrenal lesions. Adrenal lesions may be simulated by the interference of normal or pathological adjacent structures, such as the tail of the pancreas, splenic vessels, accessory spleens, enlarged lymph nodes, masses arising from the upper pole of the kidney, normal fluid-filled stomach and diaphragmatic tissue. Consequently, if there is no evidence of an adenoma in the left adrenal gland responsible for the biochemical syndrome, the other causes of primary hyperaldosteronism should be considered. First, it must be asked whether the right gland is strictly normal on MRI. If the patient has been placed in the supine position, it is possible to explore the contralateral gland laparoscopically. However, if the patient has been placed in the full lateral position, exploration of the contralateral gland is possible only by ultrasonographic retroperitoneal transcaval examination. Bilateral adrenal hyperplasia (idiopathic hyperaldosteronism) can be eliminated on the magnetic resonance image. Glucocorticoid-remediable hyperaldosteronism is another possible aetiology, although it is very uncommon³.

What should the surgeon do?

If the biochemical diagnosis is certain and there is no obvious lesion in the gland at laparoscopic exploration, the surgeon should remove the adrenal in only three circumstances:

- 1 Functional localization procedures (adrenocortical scintigraphy and/or selective adrenal venous sampling) performed before operation confirm the localization of the disease in the left gland.
- 2 Laparoscopic ultrasonography demonstrates the adenoma.
- 3 Laparoscopic ultrasonography is not available and there is a very strong suspicion of an adenoma; through a minilaparotomy using an enlarged trocar incision, the surgeon can perform a video-assisted one-handed palpation to confirm the lesion.

In all other cases the operation should be discontinued without adrenal resection and both the biochemical diagnosis and MRI should be re-evaluated.

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Non-operative treatment of abdominal gunshot injuries

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Background: Non-operative treatment is a management option that challenges the traditional mandatory laparotomy for abdominal gunshot injuries.

Methods: All published relevant clinical reports were retrieved by searching through the Medline database and manually. The theoretical arguments in favour of non-operative management as well as the results of the reviewed reports are analysed and evaluated.

Results and conclusion: Patients with proven non-penetration of the abdominal cavity can be offered conservative treatment with a satisfactory outcome. Greater caution should be exercised in the presence of a documented visceral injury until the safety of this option has been established by further clinical trials.

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Introduction

Mandatory laparotomy has traditionally been recommended for the treatment of abdominal gunshot wounds. Recently, however, a small number of studies have tested a more selective approach and non-operative treatment of abdominal gunshot injuries is now being advocated for certain subgroups of patients. While highly controversial, this management option has not emerged *de novo*. Rather, it appears as a logical development of a conservative trend that has permeated, for some time already, the treatment of abdominal trauma. The aim of this paper is to describe this evolution in trauma surgery, to examine the data derived from all available relevant studies, and to evaluate the evidence for and against this new management modality.

Conservative trends in abdominal trauma

The past four decades have been characterized by the increasing recognition that subsets of patients with abdominal trauma can be successfully treated non-operatively. The 1960s marked the turning point in favour of the policy of selective conservatism for treating abdominal stab wounds^{1,2}; such management was initially advocated against a strong background of opinion recommending mandatory laparotomy for all such cases. It was suggested, in brief, that non-operative treatment can sensibly be offered, at least for an initial observation period, to patients without signs of peritoneal irritation or blood loss. This policy has been highly successful in decreasing the rate of

non-therapeutic laparotomy and has proved, at the same time, exceedingly safe in the management of stab wounds of the abdomen³. With or without modern refinements, such as diagnostic peritoneal lavage and radiological imaging in patients not amenable to clinical evaluation alone, this approach has now become widely accepted⁴. Selective non-operative management of blunt abdominal trauma has undergone a similar evolution, a field in which advances have been biphasic. First, progress was made in selecting out for observation those patients with no significant intra-abdominal injury. For many years diagnostic peritoneal lavage served trauma surgeons well⁵; more recently, radiological imaging has been used increasingly to complement or even replace peritoneal lavage⁶. In a second phase, coinciding with the increasing availability of contrast-enhanced computed tomography (CT), significant blunt injuries to solid organs became treatable non-operatively if they fulfilled certain (mainly clinical) criteria. Hepatic trauma, in particular, has proven amenable to conservative management. Laparotomy may be avoided even in high-grade, CT documented, blunt liver injury, provided haemodynamic stability can be maintained and the presence of associated abdominal injuries requiring operation is ruled out^{7,8}.

Gunshots wounds: the gold standard

A strong consensus in favour of mandatory surgery for abdominal gunshot injuries, irrespective of clinical signs, prevailed in the 1970s and 1980s^{9–13}. These wounds were

considered to be associated with a prohibitive rate of both intra-abdominal penetration and visceral injury requiring surgery. The expectation of a negligible proportion of negative or non-therapeutic laparotomies has undoubtedly been reinforced by the experience of war surgeons, dealing mainly with high-energy missiles. Mandatory laparotomy has remained to this day the orthodox management of abdominal gunshot injury¹⁴. It was conceded long ago, however, that certainty of non-penetration of the abdominal cavity by the bullet could justify conservative treatment¹⁵, and some authors resorted to diagnostic peritoneal lavage to detect intraperitoneal injury associated with apparently superficial abdominal wounds with equivocal abdominal signs^{16,17}. Nevertheless, an aggressive policy was justified by a greater than 95 per cent risk of significant injury associated with abdominal gunshot wounds^{16,18}.

Rationale for non-operative treatment

A serious challenge to the dogma of mandatory laparotomy started in the 1990s¹⁹ and it is appropriate to consider the theoretical justification that underpins this challenge. Arguments in favour of a selective conservative approach are borrowed from the management of both stab wounds and blunt trauma. Advocates of non-operative treatment readily admit that gunshot wounds may be attended by a high rate of peritoneal penetration and, perhaps, a probability of visceral injury requiring operative repair. However, they argue, first, that there is a significant proportion of cases with either non-penetration of the abdominal cavity by the missile or with negligible intra-abdominal injury. Their analysis of earlier studies of civilian trauma reveals rates of negative or non-therapeutic laparotomy, performed for gunshot wounds, ranging from 15 to over 25 per cent^{11,20–22}; many of these patients would have sustained tangential wounds to the abdominal wall. Even in military surgery, the compilation of 1350 laparotomies carried out for war wounds sustained in Vietnam revealed a rate of negative laparotomy of 19.2 per cent²³. Thus, conservative treatment may be recommended for this subset of patients, provided that they can be identified reliably. The argument is reinforced by the demonstration in the modern trauma literature of the significant morbidity and financial burden associated with unnecessary laparotomy^{22,24–26}.

A second argument is based on the putative similarity between the visceral injuries inflicted by stabs and those caused by the low-energy gunshots encountered in civilian practice. Little might be lost by applying to gunshots the management protocol used for stab wounds, even in cases of documented peritoneal penetration. Patients with no evidence of peritonitis or haemorrhagic shock would be

subjected to an appropriate period of clinical observation at the conclusion of which their unchanged status would justify the non-operative option. Indeed, the fact that a bullet travels for longer distances in the abdomen than a knife and is more likely to cause multiple injuries should result in a more obvious clinical presentation in those initially asymptomatic patients who are destined to fail the test of initial observation. Therefore delays in identifying and operating on these patients might be expected to be shorter. While it has been claimed that clinical evaluation is unreliable for gunshot wounds^{11,16,27}, one study detailing that more than 40 per cent of patients with subsequently confirmed intra-abdominal injury were asymptomatic on admission¹¹, the proponents of non-operative treatment reject these claims as counterintuitive and biased. They argue that a pre-established management protocol of mandatory immediate intervention is unlikely to allow patient selection and identification of cases amenable to non-operative treatment.

Additional justification for non-operative management may also be adduced from the management of blunt trauma. In both penetrating and (especially) blunt trauma there has been a remarkable evolution in what is now recognized as a visceral injury requiring operative repair or ablation²⁸. The significant potential for spontaneous healing of traumatized solid organs (liver, spleen, kidney) has now been demonstrated and indications for conservative treatment for severe blunt trauma to these organs are widely accepted. So, it is argued, if a grade III or IV blunt hepatic rupture is sometimes amenable to non-operative treatment, is it unreasonable to at least consider the conservative option for a documented hepatic gunshot injury?

Clinical trials of non-operative treatment

The few reported clinical trials fall into different categories. One such category comprises studies of all-comers with an abdominal gunshot wound^{29–31}. Another encompasses collections of patients with an entrance wound in a specific region of the abdomen (the anterior abdominal wall³², the back³³, the right thoracoabdomen³⁴, the pelvic abdomen³⁵). Yet another focuses on a specific abdominal organ (liver^{36,37}, kidney³⁸). Pertinent data from these studies are summarized in *Table 1*. It is noteworthy that not a single death was reported in any of these series in patients subjected to initial observation (whether or not they required a delayed laparotomy). Morbidity was negligible except when there was a protocol violation³⁷.

The primordial role of clinical evaluation in patient selection is emphasized in all the studies. This implies availability in hospital of senior surgical staff throughout the observation period and readiness to intervene in the face

Table 1 Clinical trials of non-operative treatment of abdominal gunshot wounds

Reference	Year	Injury site	Total no.	Specialized diagnostic tests	No. having initial observation	No. managed non-operatively
Muckart <i>et al.</i> ²⁹	1990	Abdomen	111	None	22	22 (20)
Demetriades <i>et al.</i> ³⁰	1991	Abdomen	146	None	41	34 (23)
Chmielewski <i>et al.</i> ³¹	1995	Abdomen	185	CT	12	12 (6)
Demetriades <i>et al.</i> ³²	1997	Anterior wall	309	CT, IVU, laparoscopy	106	92 (30)
Velmahos <i>et al.</i> ³³	1997	Back	192	CT, IVU	131	127 (66)
Renz and Feliciano ³⁴	1994	Right thoracoabdomen	32	CT, DPL	13	13 (41)
Velmahos <i>et al.</i> ³⁵	1998	Pelvic abdomen	37	IVU, cystography, sigmoidoscopy	18	15 (41)
Demetriades <i>et al.</i> ³⁷	1999	Liver	152	CT	16	9 (6)
Velmahos <i>et al.</i> ³⁸	1998	Kidney	52	IVU	4	4 (8)

Values in parentheses are percentages. CT, contrast-enhanced computed tomography; IVU, intravenous urography; DPL, diagnostic peritoneal lavage

of even minimal changes in clinical status. Indeed the rate of non-therapeutic laparotomy in patients deemed to have failed initial observation was high, attesting to a low threshold for surgical intervention. While in the early studies^{29,30} clinical assessment was used alone (except for the addition of plain chest and abdominal radiography), in the later studies^{31–38} a variety of diagnostic modalities was employed (Table 1). The purpose of this complex diagnostic assessment was more to document the presence of injury and follow up progress rather than influence patient selection^{32–35,37,38}. A single case report of liver gunshot injury³⁶ illustrates, however, the possible use of contrast-enhanced CT in predicting failure of the non-operative approach. These diagnostic modalities were able to identify a variety of injured viscera in patients treated conservatively: lung, liver, hepatic vein, spleen, kidney, extraperitoneal portion of the bladder, vertebrae and spinal cord.

Evaluation of the policy of non-operative treatment

Even if one makes allowance for overlapping patient populations in the series from the same centre, there are now at least 300 patients who have been reported as successfully treated by conservative means. Still, this is hardly sufficient to recommend a wholesale selective conservative approach for all initially asymptomatic patients with an abdominal gunshot wound. The reviewed studies deal with various intermingled issues that need to be unravelled.

It seems that the case for conservative treatment in the particular scenario of non-penetration of the abdomen by the bullet is quite strong. Tangential parietal wounds can sometimes be very obvious. In most cases, however, the addition to clinical evaluation of various diagnostic modalities (diagnostic peritoneal lavage, ultrasonography,

contrast-enhanced CT, thoracoscopy and laparoscopy), singly or in combination, can reliably rule out abdominal penetration. It is reasonable to recommend that whenever clinical evaluation suggests a non-penetrating wound an appropriate additional diagnostic test be used. For example, a clear return of peritoneal lavage fluid in an anterior abdominal wound may serve as sufficient confirmation¹⁶. The finding at thoracoscopy of an intact left hemidiaphragm in a lower left thoracic gunshot injury is another way of ascertaining the integrity of the abdominal cavity³⁹. Similarly, a contrast-enhanced CT scan may serve to rule out the presence of both free intraperitoneal fluid and a visible visceral injury in a right 'thoracoabdominal' wound³⁴. Laparoscopy has also been recommended for anterior abdominal wounds⁴⁰, although one might wonder if substituting routine laparoscopy under general anaesthesia for mandatory laparotomy constitutes significant progress.

In other situations, however, caution must be exercised. The claims that transpelvic gunshots³⁵ and those to the back³³ are amenable to clinical assessment alone and that, as a consequence, surgery can be avoided in some patients need further corroboration. It is conceivable, though, that peritonitis developing as a result of a subtle injury low in the pelvic abdomen could be detected by careful clinical evaluation. The issue of gunshot wounds to the back, however, is a vexed one. There is still a strong body of opinion in favour of extensive diagnostic evaluation in the management of penetrating wounds to the back⁴¹ (whether these are from stab or gunshot), and concern about the possibility of missing a posterior colonic, duodenal or ureteral injury by sole reliance on clinical signs (or even by recourse to a variety of diagnostic tests) may be difficult to allay.

More importantly, the denial of a laparotomy to a patient with a documented solid visceral intra-abdominal injury

rests on even more uncertain ground. The argument based on the similarity between blunt and gunshot injuries to solid organs (liver, for example) is not convincing. There may not be a major difference between the liver shattered by blunt trauma and the hepatic disruption wrought by a bullet, but this is where the similarity ends. The major issue revolves around the presence of associated hollow visceral injury. In the blunt trauma scenario, the likelihood of such an injury is very small. In all-comers with blunt abdominal trauma, it is about 1 per cent⁴². In the subgroup of patients with a known blunt hepatic injury, associated injuries are noted in 4–15 per cent^{43,44}. In contrast, the incidence is considerably higher with penetrating trauma. In a series of patients (aged less than 19 years), there was an 80 per cent incidence of associated injury requiring a laparotomy⁴⁵. In another study, injury occurred in up to 63 per cent of cases, mostly to the gastrointestinal tract⁴⁶. From a practical point of view, this problem can be illustrated in the setting of hepatic gunshot injury. It is common for an injury of moderate severity to be associated with upper quadrant peritoneal irritation; this makes it impossible to rule out, by clinical assessment alone, an associated colonic or duodenal laceration. It is noteworthy that no single adjunctive test (such as diagnostic peritoneal lavage, CT with contrast, ultrasonography or even laparoscopy) has proved infallible in ruling out the presence of an abdominal hollow visceral injury. Demetriades *et al.*³⁷ are rightly cautious in pointing out that the 5 per cent hepatic injuries that they successfully treated non-operatively were carefully selected grade I and II liver lesions. Furthermore, concern remains about the possibility of long-term complications, such as broncho-biliary⁴⁷ or thoracobiliary⁴⁸ fistula. As for the non-operative management of documented renal gunshot injury, the same arguments for caution pertain, especially as the total reported experience amounts to only a handful of cases^{34,37,38}.

The reaction to the non-operative treatment of abdominal gunshot injury amongst the trauma fraternity has ranged from enthusiasm⁴⁹ to extreme circumspection²⁸. One must appreciate that this method of management has yet to be put to the test of reproducibility. Six^{30,32,33,35,37,38} of the nine series reviewed here emanate from the same trauma centre or have the same or similar authorship.

Conclusion

The advocates of non-operative treatment of abdominal gunshot injury have presented a valid argument for their case in the subset of patients with non-penetration of the abdominal cavity. Non-penetration can sometimes be clinically very obvious. At other times, it may require confirmation by an appropriate ancillary diagnostic test. It

may also be possible to rule out, in a totally asymptomatic patient who remains so over a certain observation period, a significant intra-abdominal visceral injury. However, penetrating extraperitoneal injuries can be treacherous. Therefore, for gunshot wounds of the back it is advisable to resort to diagnostic imaging and, in any case, to maintain a low threshold for intervention. At this stage the conservative treatment of documented gunshot injuries to solid organs (liver in particular) cannot be recommended. Non-operative management should still be subjected to a variety of trials in different centres and in well controlled clinical settings before being recommended for wider use.

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Smoking and disease recurrence after operation for Crohn's disease

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Background: There is increasing speculation about the role of smoking in the pathogenesis of inflammatory bowel diseases. The purpose of this study is to review the impact of smoking on disease recurrence after operation for Crohn's disease.

Methods: A Medline-based literature review (1966–1999) was carried out; ten studies examined the relationship between smoking and disease recurrence after operation.

Results: Approximately half of the patients were smokers at the time of operation. In most studies smoking significantly increased the risk of postoperative disease recurrence. Smokers had an approximately twofold increased risk of recurrence compared with non-smokers and the effect of smoking was dose dependent. The increased risk of recurrence among smokers was more prominent in women than in men, and a longer duration of smoking increased the risk of recurrence. Ex-smokers had a similar recurrence rate to non-smokers and giving up smoking soon after operation was associated with a lower probability of recurrence.

Conclusion: Smoking significantly increases the risk of recurrence of disease after operation for Crohn's disease, especially in women and heavy smokers. Encouraging patients to stop smoking is an important part of the management of Crohn's disease.

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Introduction

Smokers are under-represented amongst patients with ulcerative colitis and over-represented amongst those with Crohn's disease^{1–19}. The mechanisms for these differential effects remain speculative^{20–39}. Smoking is one of the most significant environmental factors to be identified in inflammatory bowel disease, both in terms of its potential relevance to disease expression and of the clear differences found between its frequency in Crohn's disease and in ulcerative colitis. In addition to the risk identified in epidemiological studies, smoking may have an adverse effect on the clinical course of Crohn's disease. However, only a few studies have examined the relationship between smoking and disease recurrence after operation^{16,40–49}. The purpose of the present study is to review the impact of smoking on recurrence of disease after operation for Crohn's disease.

Methods

Relevant publications indexed in Medline (1966–1999) were identified using the following medical subject head-

ings: inflammatory bowel disease, ulcerative colitis, Crohn's disease, smoking, surgery and recurrence. Further articles identified from the reference lists of the above searches were also reviewed. All publications about the relationship between smoking habit and recurrence rate after operation for Crohn's disease were reviewed, and the postoperative recurrence rates for smokers and non-smokers were compared. The impact of smoking on recurrence rate was also examined according to sex, disease location, dose of cigarettes and smoking duration.

Results

Smoking habit

Ten studies examined the relationship between smoking habit and disease recurrence after operation for Crohn's disease (*Table 1*)^{16,40,41,43–49}. In all studies the smoking data were obtained by postal questionnaire and/or personal interview. Patients were asked about smoking habit at the time of diagnosis of Crohn's disease, and before and after operation for Crohn's disease. They were also asked about

Table 1 Relationship between smoking and disease recurrence after operation for Crohn's disease

Reference	Year	Study period	Site of disease	Data collection	Length of follow-up	Outcome			Statistical analysis
						Non-smokers	Smokers	Ex-smokers	
Sutherland <i>et al</i> ⁴⁵	1990	1966–1983	SB + IC + LB	Questionnaire	Mean 10.8 years	Reoperation rate (n=85) 5 years 29% 10 years 41%	(n=89) 5 years 36% 10 years 70%		P=0.007 RR 2.1
Lindberg <i>et al</i> ⁴⁶	1992	No record	SB + IC + LB	Questionnaire	10 years	Reoperation rate (n=81) 26%	10 years postop (n=54) 42% (heavy smokers: >10/day)		P=0.015 RR 1.79
Martin <i>et al</i> ⁴⁰	1994	1971–1991	SB + IC + LB	No record	Mean 4.6 years	No detailed data presented			n.s.
Cottone <i>et al</i> ⁴¹	1994	1973–1991	SB + IC + LB	Questionnaire	Mean 8.2 years	(n=53) Clinical recurrence* rate 40%	(n=110) 6 years postop 73%	(n=19) 59%	P=0.006‡ RR 1.4 P=0.005‡ RR 2.0 P=0.002‡ RR 4.3
Breuer-Katschinski <i>et al</i> ⁴⁷	1996	1989–1992	SB + IC + LB	Questionnaire	No record	Reoperation rate (n=143) 5 years 26% 10 years 33%	(n=144) 5 years 43% 10 years 64%		P<0.00 RR 3.1
Cosnes <i>et al</i> ¹⁶	1996	1974–1995	SB + IC + LB	Personal interview	No record	Crude reoperation rate (n=89) 22%	(n=115) 30%		n.s.
Timmer <i>et al</i> ⁴⁸	1998	1990–1993	SB + IC + LB	Personal interview	48 weeks	Relapse† rate (n=53) 30%	48 weeks postop (n=59) 53%	(n=40) 35%	P=0.02‡ RR 2.1
Medina <i>et al</i> ⁴⁹	1998	No record	SB + IC + LB	No record	No record	Crude symptomatic recurrence rate (n=14) 86%	(n=26) 50%		n.s.
Yamamoto and Keighley ⁴³	1999	1975–1990	IC alone	Personal interview and questionnaire	Median 8.1 years	Reoperation rate (n=79) 5 years 19% 10 years 36%	(n=62) 5 years 35% 10 years 55%		P=0.007 RR 2.3
Yamamoto <i>et al</i> ⁴⁴	1999	1960–1996	LB alone	Personal interview and questionnaire	Median 18.6 years	Reoperation rate (n=36) 5 years 11% 10 years 15% 15 years 18%	(n=33) 5 years 25% 10 years 46% 15 years 52%		P=0.005 RR 3.0

SB, small bowel, IC, ileocaecal, LB, large bowel; CDAI, Crohn's Disease Activity Index; RR, relative risk, n.s. not significant *CDAI > 150, †CDAI > 150 or increase of CDAI > 60, ‡smokers *versus* non-smokers

the number of cigarettes smoked, the duration of smoking, and the reason why they changed smoking habits (if they did). A smoker was defined as a patient who had smoked at

least five (or seven) cigarettes per week for more than 1 year (or 6 months) before the time of operation. Patients who began smoking after the onset of the disease and those who

gave up smoking soon after operation were classified as smokers. An ex-smoker was generally defined as a patient who gave up smoking at least 1 year before operation. A non-smoker was defined as a patient who had never smoked, or had smoked a little and occasionally. From Table 1 it can be seen that the proportion of smokers ranged from 39 to 60 per cent^{16,40,41,43-49}. In most studies approximately half of the patients were smokers. Sutherland *et al.*⁴⁵ found that the proportion of smokers was 57 per cent among women, which was significantly higher than the 40 per cent among men. In contrast, from the study by Cottone *et al.*⁴¹, the proportion of smokers was significantly higher among men (68 versus 52 per cent). However, when all the papers in Table 1 are analysed the proportion of smokers ranged from 32 to 57 per cent in women compared with 33-68 per cent in men^{16,40,41,43-49}. There was no significant difference in the proportion of smokers between women and men in most studies.

Impact of smoking on recurrence

In most studies in Table 1 recurrence was defined as a need for reoperation after a primary operation^{16,41,43-47}. In two studies clinical relapse according to the Crohn's Disease Activity Index (CDAI) was used for the analysis^{41,48}. All except two studies^{43,44} included patients with Crohn's disease at various anatomical sites (small bowel, ileocaecal region, large bowel). On the other hand, two studies from Birmingham, UK, examined patients with ileocaecal disease⁴³ and colonic disease⁴⁴ separately. In those studies^{43,44} only patients who underwent the same surgical procedure (bowel resection with conventional sutured end-to-end anastomosis) were included in order to analyse a well defined homogeneous group of patients. Three studies^{41,42,44} examined risk factors for recurrence using a multivariate analysis including smoking habit and other clinicopathological factors (age, sex, family history of Crohn's disease, duration of disease before surgery, site of disease, preoperative or postoperative medication, indications for surgery (perforating or non-perforating disease), extent of disease (length of resected bowel), involvement of disease at the resection margin, granuloma in the resected specimen and postoperative complications).

In seven of the ten studies in Table 1, smoking was significantly associated with a high rate of postoperative relapse or recurrence compared with findings in non-smokers, the relative risk ranging from 1.4 to 4.3^{41,43-48}. In 1990, Sutherland *et al.*⁴⁵ initially reported the relationship between smoking habit and disease recurrence after operation for Crohn's disease. They found⁴⁵ a significantly higher risk of recurrence in smokers compared with non-smokers after following 174 patients for over 10 years.

Lindberg *et al.*⁴⁶ examined the effect of smoking on the localization and clinical course of Crohn's disease. They found that the accumulated number of fistulas and/or abscesses was significantly higher for smokers than for non-smokers (52 versus 37 per cent)⁴⁶. Heavy smokers (more than ten cigarettes a day) had small bowel disease more often than light smokers (ten or fewer cigarettes daily). They also found that there was a significant difference in reoperation rates at 10 years after operation between non-smokers (26 per cent) and heavy smokers (42 per cent)⁴⁶. Cottone *et al.*⁴¹ noted a significantly higher risk of recurrence among smokers in an examination of three types of recurrence using multivariate analysis (clinical, surgical and endoscopic recurrences). Ex-smokers had a similar clinical recurrence rate to non-smokers. These authors⁴¹ also examined the impact of smoking on recurrence according to sex, disease location, dose of cigarettes and smoking duration. The results are presented in the following sections of this review. Breuer-Katschinski *et al.*⁴⁷ found that many more surgical procedures were required in smokers (at least one operation in 73 per cent) than in non-smokers (39 per cent), and that multiple episodes of surgery were 10.8 times more likely in smokers. The overall frequency of fistula and/or abscess formation was higher in smokers than in non-smokers (40 versus 13 per cent respectively). The cumulative reoperation rate for recurrence was significantly higher in smokers than in non-smokers (64 versus 33 per cent at 10 years). Timmer *et al.*⁴⁸ examined the effects of smoking and oral contraceptive use on clinical relapse of Crohn's disease. At 48 weeks after operation, the relapse rate (defined as CDAI greater than 150 or an increase in CDAI of more than 60) was 30 per cent in non-smokers and 53 per cent in smokers, and the relative risk was 2.1. This difference was statistically significant. Ex-smokers did not have an increased risk; the relapse rate was 35 per cent, which was similar to the 30 per cent found in non-smokers. Two studies from Birmingham also confirmed that in patients with ileocaecal and/or colonic disease the cumulative reoperation rate for recurrence was significantly higher in smokers than in non-smokers^{42,44}. In these studies smoking was an independent significant risk factor for recurrence using a multivariate analysis. The only other factor associated with recurrence was duration of disease before operation among patients with ileocaecal disease⁴². In patients with colonic disease, smoking was the only significant factor⁴⁴. Cosnes *et al.*¹⁶ found that for female smokers the 10-year risk of immunosuppressive therapy was 52 per cent, compared with 24 per cent for non-smokers ($P < 0.001$). They also noted that the risk of surgery increased only in smokers who did not take immunosuppressive drugs¹⁶. However, there was no significant difference in the reoperation rate for recurrence between

smokers and non-smokers. Medina *et al.*⁴⁹ also failed to find a significant difference in the symptomatic recurrence rate between smokers and non-smokers after operation, but there were only 40 patients in their study. However, recurrence occurred earlier in smokers than in non-smokers (83.6 versus 155 weeks, *P* not significant). Martin *et al.*⁴⁰ reported that in an analysis of 286 patients there was no significant correlation between smoking habit and recurrence rate, but detailed data about smoking were not presented.

Sex and the impact of smoking

The impact of smoking on recurrence was compared between women and men in two studies^{45,47}. Sutherland *et al.*⁴⁵ showed that among women the reoperation rate for recurrence was 39 per cent in smokers and 18 per cent in non-smokers, the relative risk being 2.9 (95 per cent confidence interval (c.i.) 1.3–6.7). Among men the reoperation rate was 26 per cent in smokers and 24 per cent in non-smokers, the relative risk being 1.0 (95 per cent c.i. 0.3–6.3). Breuer-Katschinski *et al.*⁴⁷ found that among women the reoperation rate for recurrence was 84 per cent in smokers and 50 per cent in non-smokers, the relative risk being 3.4 (95 per cent c.i. 1.4–6.3). Among men the reoperation rate

was 44 per cent in smokers and 28 per cent in non-smokers, the relative risk being 2.3 (0.8–4.7). In both studies, the effect of smoking was stronger in women than in men.

Disease location and the impact of smoking

There are two papers that compare the effect of smoking on recurrence according to disease location^{45,47}. Sutherland *et al.*⁴⁵ found in women that the impact of smoking was stronger in small bowel disease than in ileocaecal or large bowel disease. The relative risk of recurrence in smokers was 9.2 (95 per cent c.i. 0.7–6.1) for small bowel disease, 2.6 (0.7–4.5) for ileocaecal disease and 2.2 (0.5–14.7) for large bowel disease compared with non-smokers; differences are statistically significant. In contrast, in men the strongest impact on recurrence was noted in large bowel disease. The relative risk of recurrence in smokers was 3.2 (95 per cent c.i. 0.7–6.1) for small bowel disease, 2.6 (0.7–4.5) for ileocaecal disease and 8.3 (0.5–14.7) for large bowel disease compared with non-smokers; the differences are not statistically significant, probably because of small number of patients in the subgroups. In the study by Breuer-Katschinski *et al.*⁴⁷ the effect of smoking was stronger in large bowel disease in both sexes. Among

Table 2 Impact of dose of cigarettes on recurrence

Reference	No. of cigarettes smoked per day	Outcome		P	
		Reoperation rate (%)	Reoperation RR		
Sutherland <i>et al.</i> ⁴⁵		Women	Men		
	0	17	26		
	1-10	25	40		
	11-20	40	27		
	21-30	42	29	P < 0.01 in women	
	31-50	50	—	n.s. in men	
Lindberg <i>et al.</i> ⁴⁶	0	26		Non-smokers versus heavy smokers	
	1-10	28		(> 10 per day)	
	> 10	42		P = 0.015	
Cottone <i>et al.</i> ⁴¹	0		1		
	1-15		1.60 (0.49-5.26)	Significant	
	> 15		4.44 (1.80-10.96)	P not recorded	
Breuer-Katschinski <i>et al.</i> ⁴⁷			Women	Men	
	1-10		1	1	
	11-20		2.3 (0.72-5.1)	0.9 (0.17-5.2)	n.s. in both sexes
	> 20		3.1 (0.93-7.2)	1.3 (0.46-5.8)	
Yamamoto and Keighley ⁴³	1-14	45	1		
	≥ 15	77	1.71		P = 0.02

Values in parentheses are 95 per cent confidence intervals. RR, relative risk, n.s. not significant

women, the relative risk of recurrence in smokers was 3.2 (95 per cent c.i. 0.7–7.2) for small bowel disease, 4.0 (0.8–8.5) for small and large bowel disease, and 5.6 (1.2–10.3) for large bowel disease compared with non-smokers; the *P* value was not given. Among men, the relative risk of recurrence in smokers was 2.2 (95 per cent c.i. 0.1–18.3) for small bowel disease, 3.2 (0.6–9.3) for small and large bowel disease, and 4.8 (1.0–7.8) for large bowel disease compared with non-smokers; again the *P* value was not given.

Dose of cigarettes and recurrence

The impact of dose of cigarettes on recurrence is shown in Table 2^{41,43,45–47}. In all of five studies, the risk of recurrence among smokers increased with an increase in the number of cigarettes smoked. In three of the studies, the difference was statistically significant, particularly in the report of Cottone *et al.*⁴¹, in which the relative risk of recurrence was 1.60 for light smokers (one to 15 cigarettes per day) and 4.44 for heavy smokers (more than 15 cigarettes per day) compared with non-smokers. Two of those studies reported that the effect of dose of cigarettes was stronger in women than in men^{45,47}.

Duration of smoking and recurrence

Only one study examined the relationship between duration of smoking and postoperative recurrence rate⁴¹. Cottone *et al.*⁴¹ divided their patients into three groups according to the duration of smoking: a short-duration group (less than 10 years), an intermediate-duration group (10–20 years) and a long-duration group (20–30 years). The risk of reoperation for recurrence among smokers *versus* non-smokers significantly increased according to the duration of smoking. The hazard ratio was 3.04 (95 per cent c.i. 1.07–8.60) in the short-duration group, 2.15 (0.72–6.41) in the intermediate-duration group and 5.52 (2.07–14.7) in the long-duration group compared with non-smokers. The risk of endoscopic recurrence in smokers was also increased in the long-duration group. The odds ratio was 2.6 (95 per cent c.i. 0.89–8.09) in the short-duration group, 7.3 (2.16–26.14) in the intermediate-duration group and 9.0 (1.48–70.38) in the long-duration group compared with non-smokers.

Discussion

There is increasing speculation about the role of smoking in the pathogenesis of inflammatory bowel diseases, since smokers are over-represented amongst patients with Crohn's disease and under-represented amongst those with

ulcerative colitis^{1–19}. In addition to the risk identified in epidemiological studies, smoking also has an adverse effect on the clinical course of Crohn's disease^{41–50}. Several studies have examined the impact of smoking on clinical relapse^{41,48–50} or surgical recurrence^{16,41–47}. Most are retrospective, so they suffer from recall bias during data collection, but approximately half of the patients were classed as smokers. There seems to be no significant difference in the proportion of smokers between women and men. Smokers have more symptoms and have a greater risk of recurrence after surgery than non-smokers^{41–48}. Duffy *et al.*⁵⁰ examined the risk of clinical relapse among smokers and non-smokers in 74 non-operative patients with Crohn's disease who were followed at monthly intervals for 6 months. The relapse rate, defined as CDAI greater than 150, was 84 per cent for smokers compared with 53 per cent for non-smokers, the relative risk being 1.6 (*P* < 0.01). Cottone *et al.*⁴¹ found in 182 patients that the risks of clinical, endoscopic and surgical recurrence were all increased in smokers compared with non-smokers. In their study⁴¹ endoscopic follow-up was performed 1 year after operation and data were available for 109 patients. They noted that smokers developed more severe lesions at the anastomosis, with strictures and nodular distortion, compared with non-smokers and ex-smokers⁴¹. In contrast, several studies^{16,40,49} failed to find a significant difference in recurrence rate between smokers and non-smokers. Cosnes *et al.*¹⁶ mainly examined the effect of smoking on the need for immunosuppressive drugs, and concluded that female smokers more frequently required immunosuppressive therapy than non-smokers. However, there was no significant difference in the reoperation rate for recurrence between smokers and non-smokers, probably because smokers who took immunosuppressive drugs had a low recurrence rate. So the effect of immunosuppressive therapy seemed to be more significant than smoking habit¹⁶, making it difficult to measure the exact effect of smoking on postoperative recurrence. Lautenbach *et al.*⁵¹ examined the relationship between time to recurrence after initial resection and smoking habit among patients who underwent at least two operations; they found no significant difference between smokers and non-smokers. Only the presence of perforating disease and long preoperative duration of disease significantly increased the risk of early recurrence⁵¹.

According to most publications, smokers appear to have an approximately twofold increased risk of postoperative recurrence of disease compared with non-smokers^{41–48}. In Birmingham, from a multivariate analysis, this risk was noted separately in homogeneous patients who underwent the same surgical procedures for ileocaecal⁴² and colonic⁴⁴ disease. In most studies, the effect of smoking appears to be

dose dependent^{41,43,45-47}. Furthermore, the increased risk of recurrence among smokers seems to be more prominent in women than in men^{45,47}; the dose-dependent relationship is also stronger in women than in men^{45,47}. Although for all sites of disease (small bowel, ileocaecal region, large bowel) smokers have a higher recurrence rate than non-smokers, there is no significant association between the impact of smoking on recurrence and disease location^{45,47}. Only one study examined the effect of smoking duration on recurrence and showed that a longer duration increased the risk of recurrence⁴¹.

Whether stopping smoking reduces recurrence after operation for Crohn's disease is an important issue. The authors have been unable to examine this factor, since so few of their patients have given up smoking after operation⁴²⁻⁴⁴. Cottone *et al.*⁴¹ and Timmer *et al.*⁴⁸ found that ex-smokers have a similar recurrence rate to non-smokers, and that giving up smoking soon after operation is associated with a lower probability of recurrence. In their analysis of non-operative patients, Duffy *et al.*⁵⁰ observed no increase of clinical relapse rate among ex-smokers compared with non-smokers. Encouraging patients to stop smoking ought to be an important part of management of Crohn's disease but there are few publications describing patients' knowledge of the association between smoking and their disease. From their questionnaire survey, Shields and Low-Beer⁵² found that many general practitioners and their patients with Crohn's disease were unaware that the incidence and course of the disease are influenced by smoking. Both doctors and patients need to be educated about the relationship between smoking and Crohn's disease.

Why does smoking increase the risk of developing Crohn's disease and the risk of disease recurrence after operation for Crohn's disease? Why does smoking decrease the risk of developing ulcerative colitis? Many studies provide the experimental data about the relationship between inflammatory bowel diseases and smoking²⁰⁻³⁹. These data suggest potentially important mechanisms of pathogenesis, including immune modulation^{20,21,25,26,29}, gut vascularity changes^{24,28,30,32,33}, alteration in gut mucus composition^{22,33,37}, alteration of gut permeability or perturbation in eicosanoid production^{27,33,36,38}. However, the mechanism of the effect of smoking on inflammatory bowel disease still remains unclear and further investigation is necessary.

Conclusion

Smoking significantly increases the risk of disease recurrence after operation for Crohn's disease, especially in women. The effect is dose dependent. Giving up smoking soon after operation is associated with a lower probability of

recurrence than that in smokers. Many patients with Crohn's disease are unaware that the incidence and course of the disease are influenced by smoking. Further education and encouragement of patients to stop smoking are required.

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Prognostic significance of oestrogen receptor β in breast cancer

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Background: Endocrine therapy for breast cancer is now well established and with the identification of a second oestrogen receptor, ER β , 3 years ago it is timely to review the possible significance of this receptor in breast cancer management.

Methods: An up-to-date review of the current literature concerning the role and possible implications of ER β in human breast cancer was undertaken.

Results: Wild-type and variant ER β are expressed in human breast tumours. Expression of ER β correlates with accepted prognostic indicators including lymph node status and tumour grade. Furthermore, levels of ER β messenger RNA alter during carcinogenesis and are upregulated in breast tumours that develop antioestrogen resistance.

Conclusion: ER β has potential as a novel clinical prognostic marker in breast cancer, particularly in determining tumours that are resistant to tamoxifen.

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Oestrogen receptors: a historical perspective

Historically, the concept of hormonal involvement in breast cancer can be attributed to the Glasgow surgeon, Sir George Beatson, who over a century ago suggested that 'secretions from the ovary' were responsible for tumour growth in premenopausal breast cancer¹. He showed in two cases of advanced breast cancer that a marked reduction in tumour size was produced by performing an oophorectomy¹. Beatson's astute observations were ahead of his time; it was several years before the first hormone was identified and several decades before the existence of hormone receptors was proposed. There are now substantial clinical, epidemiological and laboratory data indicating that oestrogens are both important mitogenic stimulants in breast cancer and have a significant role in normal breast physiology^{2–5}.

Oestrogen action is mediated by a nuclear receptor, the oestrogen receptor (ER). ER protein was identified in 1967⁶ and since then the most widely used technique for its measurement has been the ligand binding assay in which free receptor is recognized through its specific binding to a radiolabelled hormone⁷. This technique is considered the 'gold standard' for assessing ER status; not only does it detect receptor but information on receptor–ligand affinity (K_d values) can also be obtained. Recently, alternative

methods have become available, based on immunological analysis of ER in tissue sections by immunohistochemistry⁸ or by commercially available enzyme immunoassays (e.g. ER-ICA). ER positivity in breast cancer correlates with a more favourable prognosis and is widely used to predict endocrine response and clinical outcome^{9,10}.

Impact of molecular biology on oestrogen receptor biochemistry

With the advent of molecular biology, the sequence for the ER, a member of the steroid receptor superfamily, was published in two concurrent papers in 1986^{11,12}. The complete ER gene was cloned and analysed 2 years later¹³. For 10 years thereafter it was believed that only a single receptor was responsible for mediating the effects of oestrogens on target tissues. Although this was in contrast to other members of the superfamily of steroid–thyroid–retinoic acid receptors in which multiple family members are found¹⁴, it was accepted that only a single ER existed and much research focused on defining its clinical and biological role.

Ten years on from the cloning of the classical ER (since renamed ER α), steroid receptor biochemistry entered a new era with the cloning of a second ER, known as ER β , initially from rodent and later from human tissues^{15–17}.

Both receptors contain six functional domains which, in accord with other members of the steroid receptor superfamily, are denoted A–F¹⁴. There is high homology at the DNA (C region) and ligand (E region) binding domains (96 and 58 per cent respectively), while the A/B, hinge (region D) and F regions are not well conserved¹⁶. This is illustrated schematically in *Fig. 1*. The genes for both receptors are encoded by eight exons; these are located on different chromosomes, with ER α found on the long arm of chromosome 6 and ER β on chromosome 14q22–24¹⁸, confirming that each receptor is the product of independent genes. The tissue distribution (at least at the RNA level) and ligand binding affinity appear different for both receptors, suggesting that each may have a distinct biological role¹⁹.

Oestrogen receptor β in human breast cancer

The first demonstration of expression of ER β messenger RNA (mRNA) in the mammary gland was reported in 1997²⁰. Using reverse transcriptase–polymerase chain reaction (RT-PCR), this receptor was identified in human tumour biopsies as well as in breast cancer cell lines. Although there was no direct correlation between expression of ER α and ER β , some samples coexpressed both receptors. Subsequently, the ratio of ER α :ER β has been shown to alter with breast cancer progression²¹. This has been substantiated by the observation of increased expression of ER β in chemically transformed human breast epithelial cells²², suggesting that ER β may be important during the process of carcinogenesis. Subsequent studies have lent further support to this hypothesis.

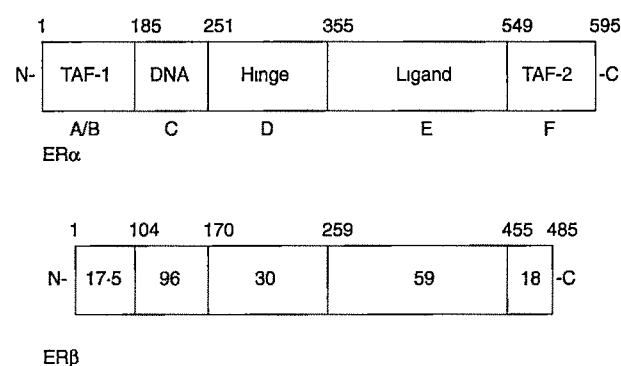


Fig. 1 Diagram of human oestrogen receptor (ER) α and ER β . Structural domains are labelled A–F. The ligand-independent transcriptional activation factor (TAF) 1 and the ligand-dependent TAF-2 are located at the amino (N) and carboxy (C) termini respectively. Numbers above each receptor refer to amino acid positions, and percentage homology between each of the functional domains is shown within the ER β structure

Work from this laboratory has compared expression of ER α and ER β in normal and malignant breast²³. While biopsies from normal breast predominantly express ER β (22 per cent of samples), this was not observed in any of the breast tumours investigated. Most breast tumours express ER α , either alone or in combination with ER β . Interestingly, lesions that coexpress ER α and ER β are significantly associated with lymph node-positive tumours that also tend to be of higher grade (both indicators of poor prognosis).

In a related study, an inverse relationship was observed between expression of ER β and progesterone receptor, generally a marker of good prognosis and an indicator of responsiveness to endocrine therapy²⁴. Lower relative expression of ER β has been reported in tumour compared with adjacent normal tissue, lending further support to the proposal that ER β expression alters during breast carcinogenesis²⁵.

The proposed significance of ER β in the endocrine response of breast tumours is further highlighted when the signalling mechanisms are considered (*Fig. 2*). Both ER subtypes can mediate gene transcription in two ways: either via a classical oestrogen response element (ERE) or via an activator protein (AP) 1 enhancer element. When signalling is mediated by the former, ligand-bound ER undergoes a conformational change and binds to the ERE as either a homodimer ($\alpha\alpha$ or $\beta\beta$) or a heterodimer ($\alpha\beta$)^{27,28}. In the latter case, ligand-bound homodimeric receptor requires the cooperation of the transcription factors Fos and Jun for transcriptional activation²⁹. When signalling is mediated via AP1, ER α and ER β signal in opposite ways. When

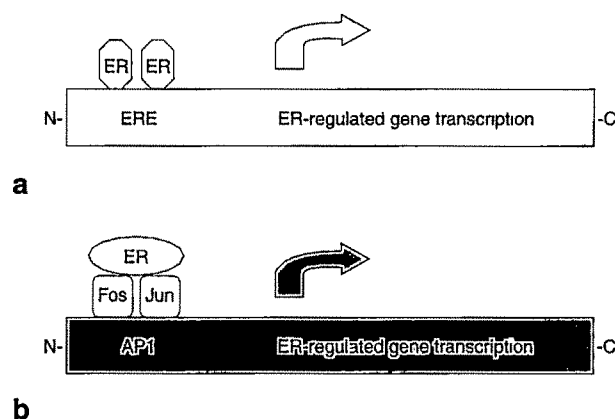


Fig. 2 Models of oestrogen receptor (ER) signalling:
 a via the classical oestrogen receptor element (ERE)
 b through an activator protein (AP) 1 element.
 Receptor activation is a consequence of ligand-induced conformational changes in ER structure²⁶

bound to ER α oestradiol activates transcription, whereas with ER β transcription is inhibited³⁰. However, all classes of antioestrogens bound to ER β are potent transcriptional activators at an AP1 site, acting as oestrogen agonists rather than antagonists³⁰. This may be important in terms of antioestrogen resistance.

Clinically, antioestrogens (notably tamoxifen) form the principal therapy for management of hormone-dependent breast cancer; around 60 per cent of all patients with breast cancer with ER α -positive lesions initially benefit³, but many eventually relapse. It has been speculated that overexpression of ER β and its interaction with AP1 may explain the failure of antioestrogen therapy in some patients with breast cancer²³. This has been addressed in a recent study in which ER β mRNA levels were determined quantitatively in primary breast tumours from patients who were tamoxifen sensitive and from those who developed tamoxifen resistance, defined as tumour recurrence while receiving tamoxifen. Using RT-PCR, the relative expression of mRNA for ER β was determined in each cohort and quantified against a known reference standard. ER β mRNA was significantly upregulated in the tamoxifen-resistant group compared with the sensitive group³¹. These data suggest that overexpression of ER β may be important in tamoxifen resistance. However, whether increased ER β expression *per se* is responsible for tamoxifen resistance or is simply a consequence of resistance remains to be determined. This should be the focus of further studies.

Oestrogen receptor splice variants

As well as wild-type ER, several isoforms of ER α and ER β generated by alternative mRNA splicing have been identified in breast tissue. ER α variant mRNAs are relatively common in breast tumours³², where they are implicated in the pathogenesis of oestrogen-dependent breast cancer³³. Such variants comprise transcripts containing single or multiple exon deletions, truncations, insertions or point mutations³². ER β variants have also been described^{34,35}. Expression of variant ER β with a 139-bp deletion of the hormone binding domain has been detected in breast tumours; it was proposed that, if translated *in vivo*, this deletion variant could result in defective ligand binding, with possible implications for acquisition of antioestrogen resistance³³. Subsequent work from this laboratory has shown this variant to be common also in normal breast tissue³⁶, and so its relevance in breast cancer remains to be determined.

More recently, five different isoforms of human ER β (ER β 1–5) have been described which differ in their C-terminal sequences³⁷. Expression of these variant mRNAs has been determined in human breast tumours; it has been

proposed that changes in the relative expression of ER β 1, ER β 2 and ER β 5 mRNAs occur during tumorigenesis²⁵. Furthermore, the relative expression of ER β 1 is inversely related to tumour grade, a feature that may be used as a marker of tumour progression²⁵. At present, however, it is not known whether these variant mRNAs are translated *in vitro* and whether they contribute to endocrine sensitivity or resistance.

Immunohistochemistry of oestrogen receptor β

The majority of published studies on ER β , including those highlighted above, have concentrated on mRNA expression; very few have considered ER β protein. It has yet to be established that expression of ER β mRNA parallels that of ER β protein. Immunohistochemical analysis of ER α in breast tumours is now a routine practice, on the results of which clinical decisions on the choice of therapy are based. From the data presented above, it may now be relevant to determine the expression of both ER subtypes, α and β . Notably, some cell lines shown previously to be negative for ER α have since been shown to express ER β ²⁰, at least at the mRNA level, and so it may well be the case that a proportion of breast tumours originally thought to be ER α -negative may in fact express ER β . This would have potential implications for clinical diagnostic purposes. Although there has been a number of studies describing the localization of ER β protein in multiple rat tissues³⁸, immunohistochemical data on ER β in human tissues have so far been more limited, possibly reflecting the difficulties in raising specific human antibodies against this protein. Nevertheless, an ER β immunoreactivity has been reported in nuclear extracts of human osteosarcoma cells and in sections of human bone (where positivity was observed in osteoblast nuclei)³⁹. A more recent study has identified ER β protein in breast cancer cell lines and in three of five breast tumour biopsies by Western blot analysis⁴⁰, providing the first indication of concordance between ER β mRNA and ER β protein in breast cancer. Although current diagnostic procedures use immunological techniques designed to detect only ER α , with the development of improved ER β -specific antibodies immunostaining for both ER subtypes may become of therapeutic value in future, particularly in predicting the response of breast tumours to endocrine therapy.

Clinical implications

The benefit of adjuvant hormonal therapy using tamoxifen is now well established in the management of breast cancer. Doubt still remains about the optimal duration of therapy, and trials are concentrating on this and on the potential

benefits of sequential antioestrogen and aromatase inhibitor therapy. Reports of tumour cell lines becoming tamoxifen dependent⁴¹ and clinical evidence of tamoxifen withdrawal leading to tumour regression⁴² result in speculation that prolonged tamoxifen therapy may be harmful in selected patients. Routine measurement of ER subtypes in specific tumours is likely to enhance our ability to individualize therapy and to offer a more selective approach in defining the most appropriate initial hormonal intervention. Receptor studies may also select subgroups in which the risks or benefits of prolonged therapy can be defined, permitting a more refined and individualized schedule of adjuvant therapy.

Concluding remarks

From the information presented above, ER β clearly has prognostic implications in the management of breast cancer. The presence of ER β in breast tumours may help to explain the differential tissue- and gene-specific effects that have been observed with oestrogens and antioestrogens. Additionally, the possible alteration in the balance of expression of ER subtypes during tumour evolution may influence the action of antioestrogens as antagonists or agonists, particularly in view of opposing downstream effects mediated by ligand-bound receptor signalling via the classical ERE, and from AP1³⁰. In the future this feature may be exploited as a tool for the development of selective oestrogen-responsive modulators to target tumours with a particular ER phenotype.

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Randomized clinical trial of haemorrhoidectomy under a mixture of local anaesthesia *versus* general anaesthesia

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Background: Application of a topical anaesthetic agent may facilitate infiltration of local anaesthetic at haemorrhoidectomy.

Methods: A randomized clinical trial of 53 consecutive patients requiring elective haemorrhoidectomy was carried out. One group underwent haemorrhoidectomy under general anaesthesia, while the second group had topical anaesthetic cream (containing lignocaine and prilocaine) applied followed by local anaesthetic infiltration for surgical anaesthesia.

Results: There were no differences between the two groups in terms of operating time, postoperative pain, nausea or vomiting, pain-free interval after operation, analgesic requirements or patients' satisfaction with the method of anaesthesia. Postoperative oxygen saturation and pulse rate were similar in the two groups.

Conclusion: Topical anaesthetic and local anaesthesia can be used effectively for haemorrhoidectomy and provide an alternative to general anaesthesia.

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Introduction

Although haemorrhoidectomy can be performed under local anaesthesia, this technique is unpopular as severe pain may be experienced during injection through sensitive perianal skin. While general and regional anaesthetics provide reliable anaesthesia, they are often associated with nausea, vomiting, hypertension, urinary retention and motor blockade of the lower limb, causing delay in mobilization so same-day discharge from hospital may not be possible.

Topical local anaesthetic (EMLA; Astra, Sodertalje, Sweden) (a mixture of lignocaine 25 mg and prilocaine 25 mg per g) has been used extensively, especially for venepuncture and intravenous cannulation¹. Other applications include simple dermatological surgery^{2,3}, minor otological surgery⁴, minor oral surgery⁵, paediatric lumbar puncture, and gynaecological, orthopaedic and urological⁶ procedures. It has proven to be effective and is well tolerated, providing satisfactory pain relief when used in these procedures. However, it should not be used in infants aged less than 6 months, who may develop methaemoglobinemia secondary to a metabolite of prilocaine.

Use of EMLA for haemorrhoidectomy has not been investigated previously. This may be because of difficulty in

providing a perianal occlusive dressing, in the absence of which the cream is ineffective. The authors have used a paraffin-impregnated gauze dressing to keep the cream in contact with the perineum. Local anaesthetic can then be injected painlessly for patients undergoing haemorrhoidectomy. A comparison was made of two groups of patients undergoing haemorrhoidectomy, one in which a mixture of EMLA and local anaesthetic was used and the other in which the procedure was performed under general anaesthesia.

Patients and methods

Fifty-three patients with symptomatic prolapsed haemorrhoids undergoing elective haemorrhoidectomy were randomized to local anaesthetic (LA group) or general anaesthesia (GA group) by the use of sealed envelopes. Only patients classified as American Society of Anesthesiologists grade 1 or 2 were included in the study. Patients' consent and ethics committee approval for the trial were obtained. Patients with a known allergy to lignocaine or paraffin were not recruited. All patients were fasted for 6 h before operation with no premedication.

In the LA group, EMLA cream was applied in the ward at least 1 h before the time of planned surgery. This was done

with the patient in the left lateral position. Ten grams of cream was applied to the piles and perianal region, followed by an occlusive dressing of gauze impregnated with paraffin. Patients were then asked to rest lying on the side. At the time of surgery, they were placed in the lithotomy position. The surgeon injected up to 15 ml 0.5 per cent bupivacaine with adrenaline into the intersphincteric planes in the perianal region. Perineal nerve blockade was not performed. If at any time a patient was intolerant of pain, the operation was continued under general anaesthesia. Alternatively, if sedation was requested, intravenous midazolam was given.

In the GA group, general anaesthesia was induced with propofol and fentanyl. Laryngeal masks were inserted in all cases. General anaesthesia was maintained with nitrous oxide, oxygen and isoflurane 2 per cent. Up to 15 ml 0.5 per cent bupivacaine with adrenaline was injected into the intersphincteric plane of the perianal region by the surgeon for postoperative analgesia. Perineal nerve blockade was not performed.

Both groups of patients had perioperative monitoring with electrocardiography, pulse oximetry and non-invasive blood pressure monitoring. All patients underwent haemorrhoidectomy with diathermy dissection without ligation of the pedicles as described previously^{7,8}, and all had three haemorrhoids excised.

The age, sex and weight of all patients was recorded. Previous experience with general, regional and local anaesthesia was noted. Patients who had had an anaesthetic previously were asked to grade their experience as pleasant, bearable or unpleasant.

In the LA group, the duration of application of the EMLA cream was recorded. The total time on the operating table and the actual time for the operation were noted. Patients were also asked to grade the degree of pain experienced during injection of local anaesthetic, introduction of the proctoscope and the surgery itself. Pain was graded as none, mild, moderate, severe or very severe. The amount of intravenous midazolam was recorded where appropriate. If conversion to general anaesthesia was required, the reasons were clearly documented.

In the GA group, the total time on the operating table, the time under general anaesthetic and the time for surgery were recorded. Any problems encountered by the surgeon or anaesthetist were noted.

After operation, all patients were sent to the recovery area of the operating theatre. Oxygen was not administered. Oxygen saturation was measured using a pulse oximeter and blood pressure was monitored using a non-invasive blood pressure cuff. Patients were asked if they experienced any pain, nausea or vomiting. They were again questioned about symptoms of pain, nausea and vomiting or giddiness 30 min later.

After return to the ward, patients were asked to inform the nurses as soon as they felt pain at the operation site. The time elapsed from surgery to the first feeling of pain was recorded. The types of analgesic required were also documented.

Patients were discharged on the evening of surgery or the next morning, according to their preference. Just before hospital discharge, patients were asked if they were satisfied with the anaesthetic, and if they would choose the same method of anaesthesia again for haemorrhoidectomy. Patients were subsequently seen 6 weeks after surgery and any complications were noted.

Statistical analysis

Data are presented as mean(s.e.m.). Fishers' exact test, χ^2 test and *t* tests were used. The level of significance was taken at $P < 0.05$.

Results

Twenty-seven patients (12 men and 15 women) were randomly assigned to the LA group. The mean age was 38 (range 23–64) years and the mean weight 57 (range 45–70) kg. Twenty-six patients (seven men and 19 women) were randomized to the GA group. The mean age in this group was 38 (range 20–74) years and the mean weight was 56 (range 41–77) kg. There was no difference in age, sex and weight, or with regard to previous experience of anaesthesia, between the two groups.

The mean time on the operating table was 16(4) min in the LA group and 18(5) min in the GA group ($P > 0.05$), and the actual operating time was 6(3) min in both groups ($P > 0.05$).

The mean duration of application of EMLA cream in the LA group was 105 (range 46–150) min. The patients' pain levels during local anaesthetic infiltration, proctoscopy and cutting by diathermy are recorded in *Table 1*. Eighteen patients had mild or no pain on injection of the local anaesthetic, 22 patients underwent proctoscopy without any complaints and 26 patients tolerated surgery by diathermy with mild or no pain. No patient required conversion to general anaesthesia. Seventeen patients were given midazolam for intraoperative sedation; ten did not require intravenous sedation.

In the GA group, the mean duration of anaesthesia (from induction to reversal) was 13(4) min. Complications related to general anaesthesia included difficulty in maintaining mask position (two patients), pain with propofol injection (one) and trauma from laryngeal mask insertion resulting in bleeding (one).

Table 1 Level of pain in 27 patients after application of topical anaesthetic cream and local anaesthetic injection

	Pain level			
	None	Mild	Moderate	Severe
At injection	7	11	8	1
Proctoscopy	22	4	1	0
Surgery	18	8	0	1

Table 2 Operation times and postoperative haemodynamic data

	Local anaesthesia	General anaesthesia
Time on operating table (min)	16(4)	18(5)
Actual time of surgery (min)	6(3)	6(3)
Oxygen saturation (%)	97.6(1.5)	97.9(1.9)
Pulse rate (per min)	78.6(12.1)	75.1(12.5)
Mean arterial pressure (mmHg)	87.7(9.8)	78.3(14.2)*

Values are mean(s.e.m.). * $P=0.01$ (Student's *t* test)

There was no difference in the oxygen saturation or pulse rates measured immediately after operation. However, there was a significant difference ($P=0.01$) in mean arterial pressure between the two groups (Table 2). In the immediate postoperative period, no patient reported any nausea or vomiting in either group. Three patients in the LA group and one in the GA group reported pain at the operation site ($P>0.05$).

Thirty minutes after surgery, two patients in the LA group and five in the GA group complained of pain. No patient complained of nausea or vomiting. One patient in the LA group and three in the GA group suffered giddiness. There was no significant difference in symptoms of pain, nausea and vomiting or giddiness between the two groups. The mean time to initial experience of pain was 5.2(2.4) and 4.4(3.0) h in the LA and GA groups respectively ($P>0.05$).

Postoperative analgesic requirements were similar in both groups. Twenty-four of 27 patients in the LA group and 25 of 26 in the GA group graded the anaesthesia as excellent or good, while the remaining patients graded it as fair. Twenty-six patients in the LA group and 25 in the GA group would undergo the same procedure again under the same anaesthesia. At 6 weeks' follow-up, no postoperative complication was reported in either group.

Discussion

Haemorrhoidectomy is most frequently performed under general anaesthesia⁸. As local infiltration of the perianal

region is painful, it is understandably unpopular among surgeons and patients. With either regional or general anaesthesia, patients are slower to mobilize, which further reduces the prospect of haemorrhoidectomy being done as a day-case procedure.

If local anaesthetic could be injected less painfully, then patients may be persuaded to undergo haemorrhoidectomy as a day case under local anaesthesia. This would not only reduce hospitalization costs for patients but also make beds available for others undergoing major surgical procedures. The cost of hospitalization and haemorrhoidectomy done under general anaesthesia is S\$1700, while the same procedure done as a day case under local anaesthesia costs only S\$700. This department performs about 1500 haemorrhoidectomies per year. It is estimated that even if only half of these patients were to be operated on as a day case under local anaesthetic, the savings would amount to a substantial S\$750 000 a year.

By using EMLA cream before infiltration of an anaesthetic, intraoperative pain is minimized and this may help local anaesthesia gain wider acceptance among patients. This study shows that application of EMLA and local anaesthetic infiltration does not take longer than general anaesthesia, and symptoms such as pain, nausea, vomiting and giddiness are not increased. The pain-free interval was also similar and both groups of patients were similarly satisfied with their respective form of anaesthesia.

The patients' oxygen saturation and pulse rate after surgery were similar in both groups. However, patients who had a general anaesthetic had a significantly lower mean arterial pressure than those randomized to local anaesthesia, although none was hypotensive. This may be due to the effects of the drugs (e.g. isoflurane) used for general anaesthesia. Therefore, in patients with medical conditions who might tolerate haemodynamic disturbance poorly, use of EMLA with local anaesthesia might be preferable.

It is concluded that use of EMLA combined with local anaesthetic infiltration is a well tolerated and effective form of anaesthesia which is comparable to general anaesthesia when used for haemorrhoidectomy. This technique has the potential to reduce hospitalization costs.

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Surgical management of polypoid lesions of the gallbladder

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Background: With improvements in ultrasonography more polypoid lesions of the gallbladder (PLGs) are being detected. The management of these is controversial.

Methods: The demographic, radiological and pathological data of 38 patients with ultrasonographically detected PLGs were reviewed. A Medline search for such lesions was performed and a review of the literature is presented.

Results: Thirty-four patients underwent cholecystectomy and four were advised against or declined operation. Of the 34 who had cholecystectomy, 11 had macroscopic and histopathologically proven PLGs. Of these, seven had cholesterol polyps, two had adenomas, one had a carcinoid tumour and one had an adenocarcinoma of the gallbladder. One patient had a histopathologically normal gallbladder. The remainder had chronic cholecystitis with or without gallstones. All of the patients with neoplastic lesions of the gallbladder had solitary polyps greater than 1.0 cm in diameter.

Conclusion: A protocol for the management of ultrasonographically detected PLGs is proposed. In this protocol it is suggested that patients with a PLG should undergo surgery if they are symptomatic, or if the PLG is 1.0 cm or more in diameter.

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Introduction

As ultrasound technology improves an increasing number of polypoid lesions of the gallbladder (PLGs) are being detected. Although some are symptomatic, others are found incidentally when the patient is scanned for another reason. The potential range of pathological lesions is large, and Christensen and Ishak have produced an ordered classifica-

tion (*Fig. 1*)¹. The distinction between benign, malignant and potentially malignant lesions is a major diagnostic dilemma and the therapeutic options for these lesions remain controversial.

The present study was initiated because an increasing number of these lesions was being identified. The aim was to study the characteristics of the patients, relate the radiological to the histopathological findings, and formulate an investigative and therapeutic protocol for future patients.

Patients and methods

The case notes of 38 patients presenting with ultrasonographically detected PLGs between January 1993 and December 1997 were reviewed for patient demography, symptoms and radiological findings. The patients were identified prospectively. In order to differentiate a PLG from a gallstone, a PLG was defined on ultrasonography as a lesion projecting into the lumen of the gallbladder which did not cast an acoustic shadow and did not move with the position of the patient (*Fig. 2*). If the patient came to surgery the macroscopic appearance was compared with the final histological diagnosis and the preoperative radiological findings.

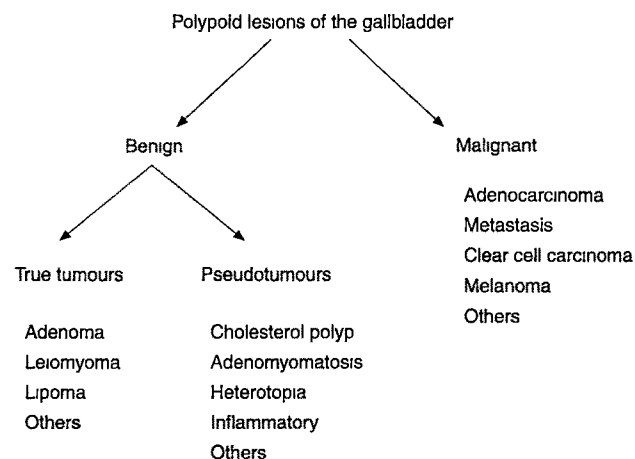


Fig. 1 Classification of polypoid lesions of the gallbladder¹



Fig. 2 Ultrasonographic image showing cholesterol polyps of the gallbladder (A) and the gallbladder wall (B)

Statistical analysis was done using a Mann–Whitney *U* test and statistical significance was taken as $P < 0.05$.

Results

There were 38 patients in the study with a mean(s.d.) age of 51.2(12.8) (range 26–80) years. There were equal numbers of men and women, with a mean age at presentation of 49.2(9.4) (range 27–66) years for men and 53.3(15.4) (range 26–80) years for women ($P = 0.19$).

Thirty-six patients were symptomatic of whom 34 had symptoms that could be attributable to the gallbladder. Thirty-two had right upper quadrant pain consistent with biliary colic and two presented with acute cholecystitis. Of the four other patients, two had scans for the investigation of lower abdominal pain and one presented with pyrexia of unknown origin, and the polyps were discovered incidentally at abdominal ultrasonography. The other patient had an episode of jaundice of unknown aetiology, although there was no biliary tract dilatation seen on ultrasonography. For these latter patients it is therefore unclear whether their symptoms were biliary in origin.

The preoperative ultrasonography reports were inconsistent in their content; the size of the PLGs was recorded in only 18 of 38 patients and the number of lesions was recorded in a similar number. From January 1993 to

December 1997 402 cholecystectomies were carried out, of which 34 were for a preoperative diagnosis of PLG. Of the 34 patients who had a cholecystectomy, there were only 11 who had macroscopic and histopathologically proven PLG in the operative specimen, giving a sensitivity of ultrasonography of 32 per cent. Of the 11 patients who had PLGs, seven had oral cholecystography in addition to ultrasonography, in five of whom the result was normal, producing a sensitivity of 29 per cent.

Histopathological analysis of the resected gallbladders revealed one normal gallbladder, 21 cases of chronic cholecystitis, seven of cholesterol polyps, one of polypoid cholecystitis and four of true gallbladder neoplasia; two patients had adenomas, one a tubulovillous adenoma with a focus of invasive adenocarcinoma within it and one had a carcinoid tumour. The malignancy rate was therefore 3 per cent (one of 34).

There was no difference in the mean age at presentation of those with chronic cholecystitis (52.3 years), neoplasia (59.3 years) or non-neoplastic polyps (52.4 years), although the only adenocarcinoma was diagnosed in the oldest patient (80 years).

All of the patients with neoplastic polyps had a solitary lesion greater than 1.0 cm in diameter, whereas those with non-neoplastic PLGs all had multiple lesions less than 1.0 cm in diameter.

All except one of the patients undergoing operation had abnormal gallbladder histology as histopathological examination showed chronic cholecystitis even when no polyps were found.

Discussion

PLGs are being found more frequently owing to improvements in ultrasound technology. Their reported frequency varies greatly, from 0.004 to 13.8 per cent of resected gallbladders^{2,3}. There was an equal sex distribution in the current series, whereas in other series there was a female predominance^{4,5} and some have found a slight male preponderance^{6,7}. PLGs occur at any age from the third decade onwards, but are more common in the fourth, fifth and sixth decades.

Risk factors for PLGs are not the same as those for gallstones, with the exception of some Japanese series that have shown a correlation with obesity⁶. There is an inverse relationship with smoking⁸.

Patients usually present with right upper quadrant pain similar to that of symptomatic cholelithiasis. Rarer presentations include acalculous cholecystitis, haemobilia⁹ and obstructive jaundice from dislodgement of a polyp¹⁰.

Cholesterol polyps are the commonest form of PLG, responsible for over 60 per cent of resected lesions.



Fig. 3 Photograph of cholesterol polyps in a gallbladder

Macroscopically the cholesterol collections in the gallbladder are easy to see (see Fig. 3). Benign true tumours and malignant tumours occur in most series with a similar frequency of 5–10 per cent⁷. This is a problem as it is very difficult to distinguish benign polyps from malignant or potentially malignant ones on ultrasonography. Ultra-sonography has a reported sensitivity of 45 to over 90 per cent^{7,11–13}; however, this was not the case in the present series. Oral cholecystography has a sensitivity of only 20 per cent in most series but may occasionally be useful. Computed tomography has a reported sensitivity for PLG of 60 per cent and endoscopic retrograde cholangiopancreatography is of little help⁷. Reports have suggested that transoesophageal¹⁴ and colour flow Doppler¹⁵ ultrasonography may aid in the preoperative diagnosis, but they are not currently widely available.

There are many lesions classified as PLG. Classification into benign and malignant, with the former further divided into true tumours and pseudotumours¹, seems the most logical. As in the present series, chronic cholecystitis is usually present as well. There is evidence that, as in the colon, there is an adenoma–carcinoma sequence in the gallbladder¹⁶. Cellular atypia and dysplasia ranging from mild to severe can be demonstrated in adenomas^{7,17} and many examples of foci of invasive adenocarcinoma in an adenoma have been found, including one in this series. There are reports of adenomas staining positive for oncofetal antigens, such as carcinoembryonic antigen and α -fetoprotein¹⁸.

Factors that increase the chances of a polyp in the gallbladder being malignant include age greater than 50 years, the presence of a single polyp, a polyp greater than 1.0 cm in size, the presence of gallstones, a sessile lesion even if less than 1.0 cm in size, and a rapid change in size on serial ultrasonography^{7,19,20}. There are a number of reports suggesting that sessile lesions less than 1.0 cm in size have an increased incidence of malignancy compared with those with a stalk²¹.

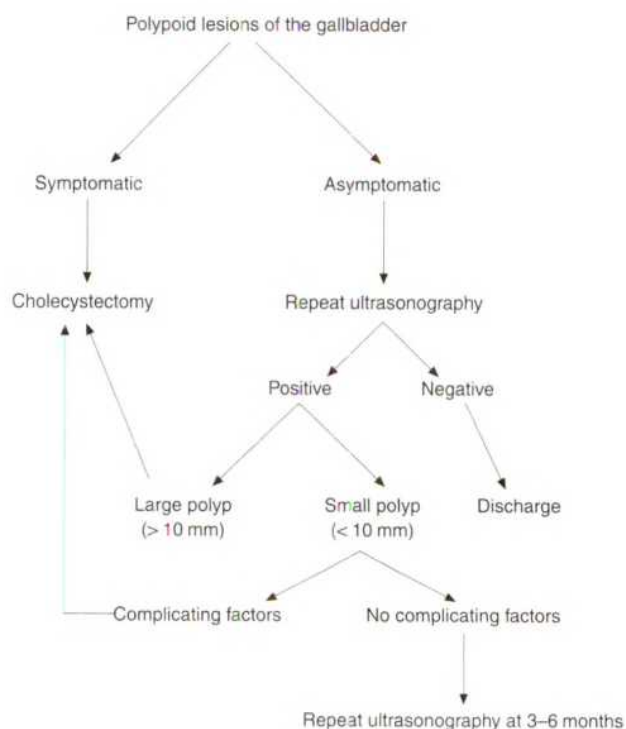


Fig. 4 Protocol for management of polypoid lesions of the gallbladder

The correct surgical management of PLG is controversial. It is widely agreed that all patients with symptomatic PLGs should be offered cholecystectomy, preferably by the laparoscopic route²². But what should be done for the asymptomatic patient? For large polyps with a greater chance of malignancy, it has been argued traditionally that patients should have an open cholecystectomy, so that a more extensive procedure can be performed if necessary. However, others have proposed that laparoscopic cholecystectomy appears to be sufficient for malignant lesions that have not breached the gallbladder serosa²², but the use of a retrieval bag is a precaution that may prevent implantation at the port sites.

In this study it was not possible to predict the nature of the PLG before operation, and it is worrying that the incidence of true neoplasia, both benign and malignant, was so high (four of 34 patients), especially given the relatively young age of the patients. However the numbers in the study were small and this may account for the rate being higher than that in series from the Far East^{11,19}.

The reason for the large number of false-positive scan results in the present series is unclear. It is possible that the patients had polypoid cholecystitis at the time of the scan which at the time of surgery did not consist of raised lesions, that gallstones were mistaken for polyps, or that some had

cholesterol polyps that had escaped the gallbladder by the time of surgery⁷.

Taking into account the inaccuracy of ultrasonography in the diagnosis of these lesions, the management protocol proposed by Boulton and Adams²³ has been modified for use with future patients (Fig. 4). All patients with a symptomatic PLG are offered laparoscopic cholecystectomy. As the sensitivity of ultrasonography is variable, asymptomatic patients are rescanned and the patient is offered a laparoscopic cholecystectomy if a PLG is identified a second time. If the repeat ultrasonographic scan does not show a PLG then a further scan is performed 6 months later and the patient is discharged if no PLG is seen a second time. Patients declining operation are followed with 6-monthly scans and if the lesion increases in size they are once again offered surgery.

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Regional and para-aortic lymphadenectomy in radical surgery for advanced gallbladder carcinoma

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Background: There have been no reports on the routine use of regional and para-aortic lymphadenectomy for gallbladder cancer. The aim of this study was to elucidate nodal status, its prognostic influence and the efficacy of lymphadenectomy.

Methods: A retrospective analysis was made of 60 patients who underwent radical resection and routine regional and para-aortic lymphadenectomy.

Results: Of the 60 patients, 73 per cent had node-positive disease and 38 per cent had positive para-aortic nodes. Postoperative survival was extremely poor in patients with minimal distant metastasis, and similarly in patients with para-aortic disease. The survival of patients with metastasis limited to the regional nodes was significantly better than that of those with distant metastasis ($P=0.029$) or para-aortic disease ($P=0.017$) and was not significantly different from that of patients with no metastasis ($P=0.82$).

Conclusion: Regional and para-aortic lymphadenectomy provides no survival benefit for patients with para-aortic disease, which has an influence on poor prognosis equivalent to that of distant metastasis. It has the potential to bring survival benefit only in selected patients with metastasis limited to the regional nodes. A sampling biopsy of the para-aortic nodes before starting radical surgery is recommended because they are involved more frequently than expected.

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Introduction

Advanced carcinoma of the gallbladder is regarded as a fatal disease; however, a few recent papers^{1–4} have reported long-term survival after radical surgery. Lymph node involvement is known to be an important prognostic indicator, and some studies have concluded that radical surgery should be considered only in the absence of involvement^{4,5}. In the tumour node metastasis (TNM) staging system⁶, N₁ (metastasis in the cystic duct, pericholedochal and/or hilar lymph nodes) is classified as stage III disease, while N₂ (metastasis in the peripancreatic, periduodenal, periportal, coeliac and/or superior mesenteric nodes) is classified as stage IVB disease (Table 1).

The route of lymphatic drainage from the gallbladder is known to be via the regional nodes to the abdominal para-aortic lymph nodes^{7–10}. The purpose of the present study was to elucidate nodal status, including regional and para-aortic lymph nodes, in advanced carcinoma of the gallbladder, and to clarify the prognostic influence of lymph node involvement and the effect of regional and para-aortic lymphadenectomy on survival.

Table 1 Tumour node metastasis staging for gallbladder carcinoma (Union Internacional Contra la Cancrum)

Stage I	T ₁	N ₀	M ₀
Stage II	T ₂	N ₀	M ₀
Stage III	T ₁ , T ₂	N ₁	M ₀
	T ₃	N ₀ , N ₁	M ₀
Stage IVA	T ₄	N ₀ , N ₁	M ₀
Stage IVB	Any T	N ₂	M ₀
	Any T	Any N	M ₁

TNM, tumour node metastasis. T₁, gallbladder wall; T₂, perimuscular connective tissue; T₃, serosa and/or one organ, or liver ≤2 cm; T₄, two or more organs, or liver >2 cm; N₁, hepatoduodenal ligament; N₂, other regional; M₁, distant metastasis

Patients and methods

Between 1979 and 1994, radical resection with no residual tumour was performed in 75 patients with pathological (p) T₂ or more advanced carcinoma of the gallbladder. Sixty of the 75 patients underwent systematic dissection of the regional nodes and para-aortic lymph nodes, and were

included in this study. There were 7, 11 and 42 patients with pT₂, pT₃ and pT₄ disease respectively. In 16 of the 60 patients, minimal distant metastases other than nodal metastasis, such as localized hepatic deposits or adjacent peritoneal seeding, were also resected. To resect all cancerous tissues, extended right hemihepatectomy was performed in 33 patients, bile duct resection in 26, pancreatoduodenectomy in 18¹¹ and combined portal vein resection in 19 patients¹².

After *en bloc* resection of the primary tumour and regional lymph nodes of the hepatoduodenal ligament and around the head of the pancreas, with skeletonization of the portal vein and hepatic artery, the para-aortic connective tissue containing lymph nodes between the levels of the coeliac artery and the inferior mesenteric artery was resected. The left renal vein and right renal artery were skeletonized, concentrating especially on the area between the aorta and the inferior vena cava. Bile duct resection or pancreatoduodenectomy was not employed for lymphadenectomy when these organs were not involved. A mean of 21.6 regional nodes and 12.4 para-aortic nodes per patient were retrieved from the fresh surgical specimen and a single representative section of each node was examined microscopically.

The authors' treatment strategy for gallbladder cancer is radical surgical excision without adjuvant therapy. No patient underwent postoperative adjuvant radiotherapy; however, five patients who requested adjuvant chemotherapy were given oral 5-fluorouracil derivatives.

The χ^2 test was used for statistical comparisons. Postoperative survival was calculated by means of the Kaplan-Meier method and differences in survival were evaluated with the generalized Wilcoxon test.

Results

The 44 patients (73 per cent) with node-positive disease included ten with pN₁ disease and 34 with pN₂ disease. Twenty-three patients (38 per cent) had positive para-aortic nodes, in nine of whom there was no macroscopic abnormality and histological examination revealed positive nodes for the first time. Although no patient with pN₀ and pN₁ disease had para-aortic lymph node metastasis, 23 of 34 patients with pN₂ disease did.

The relationship of lymph node status to primary tumour (pT) and metastasis other than nodal metastasis is shown in Table 2. The node-positive rate in patients with pT₄ disease (34 of 42) was higher than that in patients with pT₂ and pT₃ disease (four of seven and six of 11 respectively) ($P=0.042$). Similarly, the para-aortic node-positive rate in patients with pT₄ disease (18 of 42) was higher than that in patients with pT₂ and pT₃ disease (two of seven and three of 11

Table 2 Relationship of nodal status with primary tumour and distant metastasis other than nodal metastasis

	Total no.	pN ₀ (n=16)	pN ₁ (n=10)	pN ₂	
				PAN negative (n=11)	PAN positive (n=23)
pT ₂	7	3	2	0	2 (1)
pT ₃	11	5	2 (1)	1	3 (1)
pT ₄	42	8	6 (1)	10 (5)	18 (7)

Values in parentheses are numbers of patients with distant metastasis other than nodal metastasis. Pathological primary tumour (pT) and lymph node (pN) status in tumour node metastasis classification; PAN, para-aortic node

Table 3 Positive rate of individual nodes

	Rate (%)
Para-aortic nodes	38
Cystic duct nodes	30
Peripancreatic nodes posterosuperior	28
Pericholedochal nodes, inferior	27
Periportal nodes, inferior	27
Nodes along the common hepatic artery: anterosuperior	25
Nodes along the common hepatic artery: posterior	22
Nodes along the hepatic artery: inferior	18
Pericholedochal nodes, superior	17
Nodes along the hepatic artery: superior	13
Periportal nodes: superior	13
Coeliac nodes	13
Superior mesenteric nodes	12

respectively). There was no relationship between the location of the primary tumour in the gallbladder (the neck, body or fundus) and para-aortic node metastasis. All 16 patients with distant metastasis other than nodal metastasis had positive lymph nodes, nine of whom had para-aortic node metastasis. The individual lymph node-positive rates are shown in Table 3. The rate was highest in the para-aortic nodes and was more than 25 per cent in the cystic duct nodes, posterosuperior peripancreatic nodes, inferior pericholedochal nodes, inferior periportal nodes and anterosuperior nodes along the common hepatic artery. All nine patients with positive superior mesenteric nodes had para-aortic node metastasis as well.

Morbidity and mortality rates

Postoperative morbidity and mortality rates for all 60 patients were 53 and 17 per cent respectively. Eight of ten patients who died in hospital had undergone extended right hepatectomy after preoperative percutaneous transhepatic biliary drainage and died from postoperative hepatic failure. No postoperative complications were related directly to regional and para-aortic lymphadenectomy.

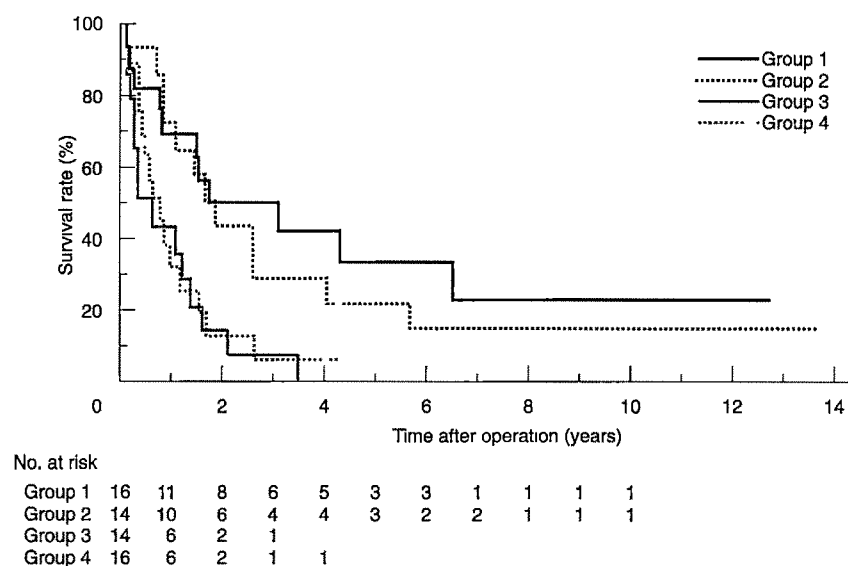


Fig. 1 Postoperative survival in patients with no metastasis (group 1), positive regional nodes alone (group 2), positive para-aortic nodes and no distant metastasis (group 3) or minimal distant metastasis other than nodal metastasis (group 4). $P=0.017$ (group 2 versus 3), $P=0.029$ (group 2 versus 4) (generalized Wilcoxon test)

Survival

Postoperative survival was extremely poor in patients with minimal distant metastasis other than nodal metastasis, regardless of pT or pN stage, with a 1-year survival rate of 38 per cent and median survival time of 8.3 months. In spite of there being no distant metastasis, postoperative survival was similarly poor in patients with positive para-aortic nodes (1-year survival rate 43 per cent, median survival 5.8 months) (*Fig. 1*). The postoperative survival rate of patients with positive regional nodes alone was significantly better than that for patients with minimal distant metastasis or with positive para-aortic lymph nodes ($P=0.029$ and $P=0.017$ respectively), and was not significantly different from that for patients with no metastasis ($P=0.82$) (*Fig. 1*).

Sites of recurrence

Sites of recurrence after radical resection with regional and para-aortic lymphadenectomy were identified by autopsy, relaparotomy or diagnostic imaging in 14 of 23 patients with para-aortic node metastasis and 19 of 37 patients with negative para-aortic nodes. The para-aortic node area was the most frequent site (six of 14), followed by the neck and mediastinal nodes (five of 14), abdominal seeding (five of 14) and the liver (three of 14) in patients with para-aortic node metastasis. By contrast, in patients without positive para-aortic node metastasis there was no nodal recurrence and predominant sites of recurrence were abdominal seeding

(nine of 19), local recurrence (six of 19) and the liver (five of 19).

Discussion

Lymph node metastasis in patients with carcinoma of the gallbladder is regarded as a strong indicator of poor prognosis^{13–15}. According to Bartlett *et al.*¹, no patient with pT₂ or more advanced gallbladder carcinoma with node-positive disease survived for 2 years, in contrast to the 5-year survival rate of 81 per cent for patients with node-negative disease. Benoist *et al.*⁴ also reported, in patients with pT₂ or more advanced disease resected for cure, a 1-year survival rate of zero for patients with node-positive disease compared with a 5-year survival rate of 43 per cent for patients with node-negative disease. However, a few recent studies^{2,3,16–18} have reported long-term survivors after radical surgery for node-positive disease. Tsukada *et al.*³ reported 15 5-year survivors after radical resection for node-positive disease and a 5-year survival rate of 31 per cent for patients with node-positive disease. Chijiwa *et al.*¹⁸ also reported four 5-year survivors with node-positive disease and a 5-year survival rate of approximately 30 per cent for patients with pN₁ disease¹⁹. These studies suggest the importance of systematic lymphadenectomy for selected patients with advanced gallbladder carcinoma.

The para-aortic lymph nodes are regarded as the final nodes in the abdominal lymphatic route from the gall-

bladder via the pericholedochal nodes and the nodes posterior or superior to the head of the pancreas⁸⁻¹⁰, and are involved in 19-26 per cent of advanced gallbladder carcinomas^{2,3}. However, the surgical efficacy of regional and para-aortic lymphadenectomy was unclear, because there have been no studies in which para-aortic lymphadenectomy has been performed routinely.

The present study, with routine use of regional and para-aortic lymphadenectomy, showed an unexpectedly high para-aortic node-positive rate of 38 per cent. This result does not indicate skip metastasis because all patients with para-aortic node metastasis also had positive nodes in the various regional areas. Postoperative survival for patients with positive para-aortic nodes without distant metastasis was as poor as that for patients with distant metastasis such as hepatic or peritoneal metastasis. Para-aortic lymphadenectomy does not therefore provide a survival benefit for patients with positive para-aortic node metastasis, which should be included in M₁ as in the present TNM staging system. Other studies^{2,3} have also revealed no 5-year survivors with para-aortic node metastasis except for one rare case report²⁰. Although there has been no evidence other than postoperative survival so far, the para-aortic nodes should be considered sentinel nodes of subclinical distant metastasis or systemic disease. When distant metastasis and para-aortic nodes were negative, however, postoperative survival for patients with positive regional nodes alone, including N₂ nodes, was significantly better than that for patients with positive para-aortic nodes and was not significantly different from that for patients without any metastasis. These results show that systematic lymphadenectomy has the potential to bring survival benefit in selected patients with pN₁ and pN₂ disease without para-aortic node metastasis. Among various nodes in N₂, the peripancreatic and periportal nodes, including nodes along the common hepatic artery, are most frequently involved and are important for regional lymphadenectomy. Because the coeliac and superior mesenteric nodes were less frequently involved and all patients with positive superior mesenteric nodes also had para-aortic metastasis, resection of these nodes seems to be less valuable. Shimada *et al.*² reported no 5-year survivors with positive coeliac or superior mesenteric nodes despite some 5-year survivors with pN₂ disease.

In the present series, 30 patients had developed obstructive jaundice due to hilar hepatic involvement, requiring extended right hepatectomy for complete removal of cancerous tissues. A major hepatectomy of the jaundiced liver led to eight postoperative deaths from hepatic failure. This high mortality rate has been decreasing since the introduction of preoperative transhepatic portal vein embolization, which causes hypertrophy of the future remnant liver^{21,22}.

In conclusion, regional and para-aortic lymphadenectomy does not provide a survival benefit for patients with advanced gallbladder carcinoma with para-aortic node metastasis, but may benefit selected patients with metastasis limited to regional nodes. It is recommended that a sampling biopsy of the para-aortic nodes should be performed before starting radical resection.

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Pancreaticojejunostomy *versus* pancreaticogastrostomy in reconstruction following pancreaticoduodenectomy

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Background: Pancreaticogastrostomy (PG) after pancreaticoduodenectomy has been reported to have a lower incidence of pancreatic fistula than pancreaticojejunostomy (PJ) but this was not confirmed in a recent prospective randomized study.

Methods: Different methods of reconstruction after pancreaticoduodenectomy were used between January 1994 and January 1999 in two university-affiliated hospitals, PJ ($n = 69$) in one hospital and PG ($n = 73$) in the other. Operations at both hospitals were performed by the same surgical team. All pancreatic anastomoses were carried out in two layers with pancreatic duct stents. Pancreatic fistula was identified by the presence of more than 1000 units/l of amylase-rich fluid in the drains 7 days or more after operation, by radiography from the pancreatic duct stent and by water-soluble contrast upper gastrointestinal studies.

Results: The two groups of patients were similar in terms of age, sex, findings at preoperative assessment, disease status, operative time, intraoperative blood loss and nature of non-tumorous pancreatic tissue. The amylase level in ascites at 7 days after operation was significantly lower after PG than PJ ($P = 0.032$). The incidence of pancreatic fistula in the PG group (zero) was significantly less than that after PJ (13 per cent) ($P = 0.014$). Intra-abdominal haemorrhage and intra-abdominal abscess occurred in three (4 per cent) and four patients (6 per cent) respectively, with two hospital deaths (3 per cent) in the PJ group, but these complications did not occur after PG.

Conclusion: This controlled clinical study supports the hypothesis that PG is safer than PJ, particularly with regard to the incidence of pancreatic fistula.

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Introduction

Pancreaticoduodenectomy has been the standard operation for resection of periampullary disease. Pancreaticojejunostomy (PJ) is generally used to reconstruct the digestive tract and remnant pancreas. Waugh and Clagett¹ devised the pancreaticogastrostomy (PG) in 1946 as an alternative to PJ. Although PG was successful, the procedure did not become popular. However, it has recently been reintroduced as a useful procedure associated with a lower incidence of pancreatic fistula than PJ^{2–4}. Unfortunately these two reconstructions were performed sequentially, not randomly or alternatively^{4,5}, and only one comparative study has been carried out⁶.

The present study examined the results of both methods of reconstruction after pancreaticoduodenectomy in two university-affiliated hospitals.

Patients and methods

The two hospitals have similar numbers (70 *versus* 80) of surgical beds available for gastrointestinal patients and surgical facilities. A plan was established regarding pancreatic–enteric anastomosis after pancreaticoduodenectomy: PJ was used in all the patients admitted to one hospital who underwent pancreaticoduodenectomy and PG was used in all such patients in the other. This study was approved by the institutional review board and written consent was obtained from the patients enrolled.

Pancreaticoduodenectomy was performed in 158 consecutive patients between January 1994 and January 1999 at the two hospitals. Of these 158 patients, 16 were excluded from the study because hepatectomy or partial resection of a major vessel was combined with the pancreaticoduodenectomy. Reconstructive methods following pancreaticoduo-

denectomy were evaluated in the remaining 142 patients, 69 patients in one hospital and 73 in the other.

There were 95 men and 47 women with a mean(s.d.) age of 59.2(12.5) years. The indications for pancreaticoduodenectomy were malignant tumours in 124 (87 per cent) (57 of the pancreas head, 42 lower bile duct, 20 Vater papilla, four gallbladder and one duodenal cancer) and benign disease in 18 (13 per cent) (16 chronic pancreatitis and two lower bile

duct stricture). Some 123 patients had a conventional pancreaticoduodenectomy (Whipple operation) and 19 underwent pylorus-preserving pancreaticoduodenectomy (PPPD). In the PJ group, PPPD was performed in five of seven patients with chronic pancreatitis and one with gallbladder cancer. In the PG group, PPPD was performed in nine patients with chronic pancreatitis, three with gallbladder cancer and one with pancreatic head cancer (chronic pancreatitis was diagnosed before operation). The operations in both hospitals were performed by the same team of hepatobiliary-pancreatic surgeons throughout the study.

Pancreatic stump management

Division of the pancreas was completed by electrocautery; the cut surface was not sutured but haemostasis was performed. The pancreatic duct was freed for a short distance (4–5 mm) and a pancreatic duct tube (Sumitomo Bakelite Medical, Tokyo, Japan) was inserted 3–4 cm into the lumen of the pancreatic duct. The duct and the tube were sutured together using 4/0 silk.

Pancreaticojejunostomy

A two-layered end-to-side anastomosis was constructed with a duct-to-mucosa anastomosis with interrupted 4/0 absorbable sutures reinforced by a seromuscular-parenchymal layer of 3/0 nylon and a transanastomotic pancreatic duct tube exiting through the jejunum proximal to the anastomosis and abdominal wall (*Fig. 1a*).

Pancreaticogastrostomy

An invagination anastomosis was constructed with two layers of interrupted 3/0 absorbable sutures from an

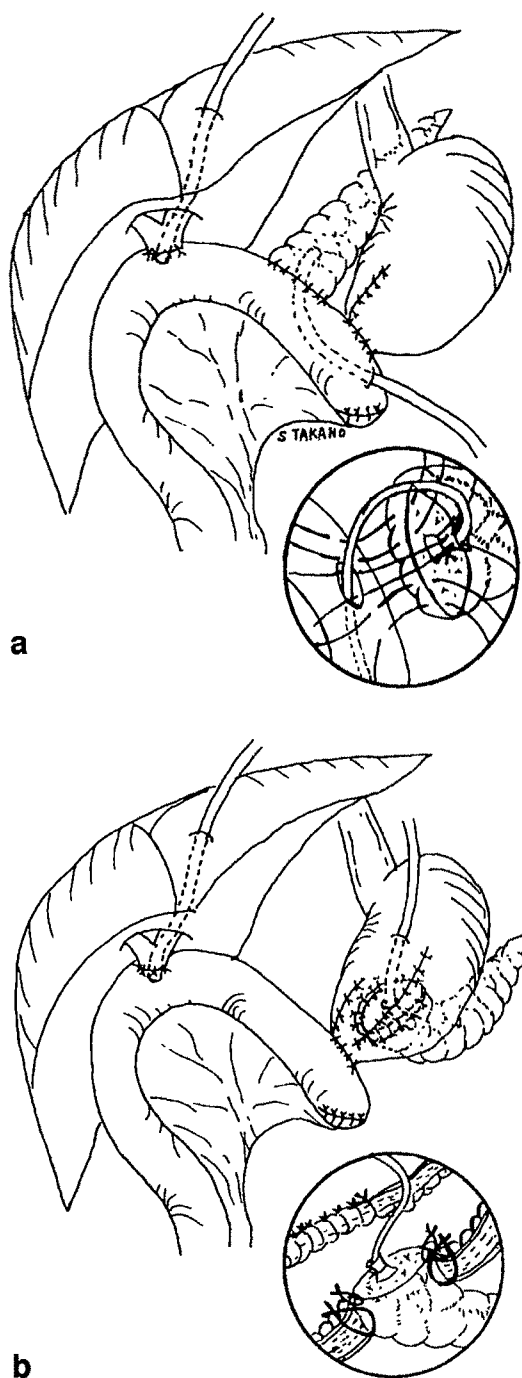


Fig. 1 Two types of reconstruction of pancreatic, biliary and intestinal continuity following pancreaticoduodenectomy.

a A pancreaticojejunostomy is created by two-layered end-to-side anastomosis with duct-to-mucosa interrupted 4/0 absorbable sutures reinforced by a seromuscular-parenchymal layer of 3/0 nylon. A pancreatic duct tube is brought out through an opening in the jejunum.

b Pancreaticogastrostomy implants the pancreatic stump into the stomach via a gastrotomy. Interrupted 3/0 absorbable sutures are placed circumferentially around 1 cm below from the stump of the pancreas and a full thickness of the posterior gastric wall through an anterior gastrotomy, and interrupted 3/0 absorbable sutures are placed between the posterior gastric mucosa/submucosa and circumferentially around the stump of the pancreas. The pancreatic duct tube is brought out through the anterior gastric wall.

anterior gastrotomy and with a pancreatic duct tube exiting through the stomach and abdominal wall (*Fig. 1b*).

Other anastomoses

Choledochojejunostomy and end-to-side gastrojejunostomy were performed in all patients and in the same manner; fibrin glue was not used in any patient. All choledochojejunal anastomoses were stented by a retrograde transbiliary duct drainage tube (RTBD) (Sumitomo Bakelite Medical). Two closed suction drains, one by the pancreatic anastomosis and one by the choledochojejunostomy, were inserted routinely.

Postoperative management

The levels of total bilirubin and amylase in fluid from the two drains were recorded once every 2 days for at least 10 days after operation. In all patients, a pancreatic ductogram and a cholangiogram were obtained through the pancreatic duct stent and RTBD respectively, and a water-soluble contrast upper gastrointestinal study was performed to assess possible leakage or obstruction at any of the three reconstructive anastomoses on day 7 after operation. Pancreatic fistulas were identified in patients with a PJ by radiography from the pancreatic duct stent or defined as more than 1000 units/l of amylase-rich fluid from the drains on or after postoperative day 7. Fistulas in patients who underwent PG were identified by a water-soluble contrast upper gastrointestinal study or more than 1000 units/l of amylase-rich fluid. In the absence of a pancreatic fistula, the pancreatic duct stent in all patients was removed on day 21 after operation.

Statistical analysis

Univariate analysis was performed with Student's *t* test for continuous variables and χ^2 test for categorical variables. $P < 0.05$ was considered significant.

Results

PJ was performed in 69 patients and PG in 73. There was no significant difference in mean age, sex ratio, preoperative clinical data or incidence of PTBD (*Table 1*). The indication for pancreaticoduodenectomy was similar between the two groups (*Table 2*). The type of pancreaticoduodenectomy performed (Whipple operation or PPPD) did not differ significantly between the two groups. There were no significant differences in the ratio of the pancreatic duct diameter (3 mm or less or more than 3 mm) and the pancreas texture (soft or hard) between the two groups. There were

Table 1 Preoperative data

	PJ (n=69)	PG (n=73)
Age (years)	59.8(9.9)	58.8(15.0)
Sex ratio (M:F)	51:18	44:29
Haemoglobin (g/dl)	12.7(1.7)	12.1(2.1)
Albumin (g/dl)	3.9(0.4)	3.7(0.4)
AST (units/l)	29.4(19.4)	39.5(36.2)
ALT (units/l)	52.3(44.4)	52.9(59.6)
FBS (mg/dl)	115.9(41.7)	122.7(36.1)
Total bilirubin (mg/dl)	1.5(1.7)	2.1(1.5)
PTBD		
Yes	44	50
No	25	23

Values are mean(s.d.). PJ, pancreaticojejunostomy; PG, pancreaticogastrostomy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FBS, fast blood sugar; PTBD, percutaneous transhepatic bile duct drainage. PTBD was routinely performed in each patient with obstructive jaundice as the preoperative management. There were no significant differences between the two groups.

Table 2 Indications for pancreaticoduodenectomy

	PJ (n=69)	PG (n=73)
Pancreas head cancer	35 (51)	22 (30)
Distal bile duct cancer	18 (26)	24 (33)
Vater papilla cancer	7 (10)	13 (18)
Chronic pancreatitis	7 (10)	9 (12)
Gallbladder cancer	1 (1)	3 (4)
Duodenal cancer	1 (1)	0 (0)
Lower bile duct stricture	0 (0)	2 (3)

Values in parentheses are percentages. PJ, pancreaticojejunostomy; PG, pancreaticogastrostomy. There were no significant differences between the two groups.

Table 3 Intraoperative data

	PJ (n=69)	PG (n=73)
Pancreaticoduodenectomy		
Whipple operation	63	60
PPPD	6	13
Pancreatic duct diameter		
≤ 3 mm	21	31
> 3 mm	48	42
Pancreatic texture		
Soft	28	33
Hard	41	40
Operative time (min)	431(116)	386(106)
Estimated blood loss (g)	1419(885)	951(809)
Blood transfusion (ml)	441(590)	239(344)

Values are mean(s.d.). PJ, pancreaticojejunostomy; PG, pancreaticogastrostomy. PPPD, pylorus-preserving pancreaticoduodenectomy. There were no significant differences between the two groups.

Table 4 Postoperative amylase levels, complications and deaths

	PJ (n=69)	PG (n=73)	P
Amylase in ascites (units/ml)*	16 154(51 520)	593(2607)	0.032†
Complications			
Pancreatic fistula	9	0	0.014‡
Intra-abdominal haemorrhage	3	0	n.s.‡
Intra-abdominal abscess	4	0	0.036‡
Biliary leakage	2	0	n.s.‡
Gastric haemorrhage	0	2	n.s.‡
Ileus	3	1	n.s.‡
Stenosis of gastrojejunostomy	0	1	n.s.‡
Death	2	0	0.1429‡

Values are mean(s.d.) *On day 7 after operation. PJ, pancreaticojejunostomy; PG, pancreaticogastrostomy. n.s., Not significant

†Student's *t* test; ‡ χ^2 test

also no significant differences between the two groups in operation time, amount of blood lost or amount of blood transfused (Table 3).

Table 4 details the amylase levels in ascites on day 7 after operation, major complications and deaths. Only the amylase level, and the incidence of pancreatic fistula and intra-abdominal abscess differed between the two groups ($P < 0.05$). Pancreatic fistula occurred in nine patients (13 per cent) after PJ but in none after PG ($P = 0.014$). Two patients died after PJ. The cause of death was related to the intra-abdominal haemorrhage associated with pancreatic fistula.

Discussion

Yeo *et al.*⁶ published an extremely high rate (12 per cent) for the incidence of pancreatic fistula after PG, a frequency that was not reported previously. According to other reports, the leakage rate after PG has been thought to be quite low, at 0–4 per cent, with a mortality rate of almost 0 per cent^{2–5,7}. Furthermore, this prospective randomized comparison of PJ and PG revealed no difference in the incidence of pancreatic fistula. The present study examined this issue by dividing the patients into two groups, a PJ group and a PG group, for which the same surgical team conducted all operations during the same period. The pancreatic fistula rate was 13 per cent with PJ and zero with PG. In the earlier series⁶, PG was performed in 83 per cent of patients who underwent PPPD. The majority of previous studies that have described low pancreatic fistula rates were based on PG after conventional pancreaticoduodenectomy (Whipple operation). In the present series, no patient who underwent PJ or PG after PPPD (six and 13 patients respectively) developed a pancreatic fistula. Therefore, it is unlikely that PPPD accounts for the high incidence of pancreatic fistula. With respect to the surgical PG

technique, Yeo *et al.*⁶ performed a two-layer anastomosis without using a stent, whereas an implantation method with a stent was used in this study. In other published reports, the pancreatic fistula rate associated with the same PG reconstruction technique as employed by Yeo *et al.*⁶ is 0–4 per cent^{3,7,8}. Many studies have reported a reduction in pancreatic fistula rate when a pancreatic duct stent is used in the pancreas–gastrointestinal tract anastomosis. This stent is especially useful in patients with a non-dilated duct or normal pancreatic tissue who have a high risk of pancreatic fistula^{9,10}.

In recent review of published reports, the incidence of pancreatic fistula after PJ ranges from 8 to 18 per cent^{10–14}. However, in more recent studies, lower rates of pancreatic fistula and death have been reported^{15,16}. Pancreatic fistulas prolong hospitalization markedly. Most patients with intra-abdominal abscess and haemorrhage have a prior pancreatic fistula, and these complications become life threatening. The merit of PJ is that pancreatic enzymes are activated, and digestion and absorption take place more physiologically. The disadvantage is that if a leak occurs, the activated pancreatic enzymes may lead to massive bleeding which may be life threatening. The disadvantage of PG is that the pancreatic enzymes are not readily activated and the pancreatic duct may be occluded by the gastric mucosa, which may result in impaired digestion and absorption. The advantage is that the incidence of pancreatic leakage is low because the anastomosis is made with the thick and richly vascular gastric wall. Even if leakage does occur, it does not lead to life-threatening complications because the pancreatic enzymes are hardly activated. In present series, two patients who had undergone PJ died after operation. The cause of death was related to intra-abdominal haemorrhage associated with pancreatic fistula. In the PG group, however, intra-abdominal abscess and haemorrhage were not observed after pancreaticoduodenectomy. The mortality rate was zero and no patient required a repeat operation.

According to the statistical analysis reported by Yeo *et al.*⁶, lack of experience (in terms of years) on the part of surgeons is a risk factor for pancreatic fistula. In the present series, all operations were performed by specialist surgeons with at least 15 years of postgraduate experience in hepatobiliary–pancreatic surgery.

Several reports have been published comparing PJ and PG in pancreatic–enteric anastomosis. Yeo *et al.*⁶ conducted the first proper prospective randomized study. The present study was not a perfect prospective randomized study but compared PJ and PG performed during the same period in two hospitals staffed by highly experienced surgeons. All other enteric anastomoses were performed almost identically. Under these conditions, PG was accompanied by better clinical results than PJ, and there was no pancreatic

fistula in the PG group. It is concluded that PG is preferable to PJ for pancreatic reconstruction after pancreaticoduodenectomy.

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Changes in pancreatic resection for chronic pancreatitis over 28 years in a single institution

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Background: Because of advances in knowledge over recent years there is reason to believe that surgical attitudes towards patients with chronic pancreatitis may have changed.

Methods: Some 547 patients were treated surgically for chronic pancreatitis from 1971 to June 1998. Anastomoses were performed in 80 per cent (438 patients) and resections in 20 per cent (109 patients). Indications and type of operation were analysed, as were mortality and morbidity rates and long-term follow-up results, in patients undergoing resection both over the period as a whole and after dividing the series into two subperiods of 14 years.

Results: In the second 14-year period, there was a significant reduction in the percentage of resections compared with anastomoses (28 per cent (69 of 244 patients) *versus* 13 per cent (40 of 303); $P < 0.0001$), and a significant change in the type of resection with a substantial increase in resections of the head compared with those of the body and tail. Statistically significant reductions occurred in operating times, number of units of blood transfused (mean(s.d.) 4.7(3.6) *versus* 1.2(1.6) units; $P = 0.0001$) and mean hospital stay (18 *versus* 14 days for pylorus-preserving and 12 *versus* 8 days for left pancreatectomy with splenectomy; $P < 0.01$); mortality and morbidity rates also tended to decrease, but not significantly.

Conclusion: A different pattern has emerged over the years as regards both the type and number of resections performed.

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Introduction

In the surgical management of chronic pancreatitis, pain has remained the main indication for surgical treatment over the years. The different physiopathological interpretations, ductal–hypertensive^{1–3} or parenchymal–nervous^{4,5}, are the theoretical basis for anastomosis^{6,7} and resection^{8–13} respectively. One unquestionable advantage of opting for resection is that it can be performed in all patients regardless of the presence of a pseudocyst and/or of an adequately dilated pancreatic duct^{14,15}. Consequently, even in series described by surgeons who are convinced that the anastomotic approach, when possible, is the treatment of choice, there are a certain percentage of resections.

Although the physiopathological interpretation of pain in chronic pancreatitis is still open to question, over the years there have been several advances in knowledge of the natural history of the disease^{16–18}, preoperative and postoperative support measures have improved, and surgical experience has increased, as has the ability to diagnose rarer causes of the disease^{19–23}. Advances in knowledge have overlapped in

the course of time with no precise cut-off points between one and the other. In clinical practice, however, they may be expected to have modified the indications for resection, and improved surgical outcomes in terms both of morbidity and mortality rates over the years.

The aim of the present study was to test this hypothesis by analysing the number and type of resections performed, the mortality and morbidity rates, and long-term follow-up results.

Patients and methods

From January 1971 to June 1998, a total of 882 patients with a firm diagnosis of chronic pancreatitis were studied prospectively in this unit. Chronic pancreatitis was diagnosed on the basis of a diagnostic evaluation including clinical, laboratory and instrumental findings that represented the gold standard for diagnosis of this disease at the various observation times over the years. Since 1976 all patients have been submitted to abdominal computed tomography and/or ultrasonography and to endoscopic

retrograde cholangiopancreatography, when considered necessary. The patients were asked to return for periodic clinical and instrumental check-ups, and monitoring of their lifestyles; those failing to attend for three successive annual check-ups were regarded as drop-outs^{24,25}.

Of the 882 patients, 547 (62 per cent) underwent pancreatic surgery. In 438 cases (80 per cent) the operation involved an anastomosis and in 109 cases (20 per cent) a resection. These latter patients are the subject of the present study.

Table 1 gives the main demographic and preoperative characteristics of the patients undergoing resection. In particular, the pancreatic duct, as measured by intraoperative pancreatography, was not dilated in 37 patients (34 per cent); dilatation was complete in 37 and sectorial in 35 of the remaining 72 patients.

Table 1 Main characteristics of 109 patients with chronic pancreatitis undergoing pancreatic resection

	Total (n=109)	1971–1984 (n=69)	1985–1998 (n=40)
Sex ratio (M/F)	96/13	61/8	35/5
Age (years)*	41 (14–78)	34 (14–57)	51 (31–79)
No. of smokers†	82 (75)	57 (83)	25 (62)
Smoking (cigarettes/day)‡	21 (11)	20 (10)	23 (12)
No. of drinkers†	72 (66)	46 (67)	26 (65)
Alcohol (g/day)‡	128 (73)	137 (79)	98 (52)
Body-weight (kg)‡	58 (10)	57 (10)	60 (9)
Diabetes mellitus†	19 (17)	10 (14)	9 (22)
Bile duct dilatation†	15 (14)	11 (16)	4 (10)
Gallstones†	18 (17)	15 (22)	3 (8)
Dilated Wirsung's duct§	72 (66)	48 (70)	24 (60)
Calcifications†	52 (48)	40 (58)	12 (30)
Pseudocyst†	52 (48)	45 (65)	7 (18)

*Values are mean (range), †values in parentheses are percentages; ‡values are mean (s.d.). §More than 6 mm

Table 2 Surgical indications in 109 patients with chronic pancreatitis undergoing pancreatic resection

	Total (n=109)	1971–1984 (n=69)	1985–1998 (n=40)
Pain	59 (54)	43 (62)	16 (40)
Suspected carcinoma	13 (12)	3 (4)	10 (25)
Pseudocyst	13 (12)	8 (12)	5 (12)
Jaundice	9 (8)	7 (10)	2 (5)
Cystic dystrophy of the duodenal wall	6 (6)	0 (0)	6 (15)
Internal fistula	5 (5)	4 (6)	1 (2)
Haemorrhage	4 (4)	4 (6)	0 (0)
Total	109 (100)	69 (100)	40 (100)

Values in parentheses are percentages

The aetiology of the chronic pancreatitis was alcoholic in 72 patients (66 per cent) and obstructive in 20 (18 per cent), while in 17 patients it was either unknown or the disease had a rarer cause. For the diagnosis of obstructive pancreatitis, the pancreatographic criterion of uniform dilatation of the main pancreatic duct upstream of an obstruction was used, and since 1989 the obstructive category has included 15 patients (14 per cent) with cystic dystrophy of the duodenal wall. In addition, 25 patients (23 per cent) had already undergone surgery. The operation had been a gastric resection for the presence of peptic disease in 12 patients and laparotomic cholecystectomy in nine, while four patients (4 per cent) had already undergone pancreatic surgery (two cystojejunal anastomoses, one pancreaticojejunal anastomosis and one left pancreatectomy).

Table 2 summarizes the main indications for surgical treatment.

Statistical analysis

The data were analysed statistically using the Friedman test, and comparison between groups was done using the Mann-Whitney test with correction for multiple comparisons. χ^2 or Fisher's tests were used for qualitative data. $P < 0.05$ was considered statistically significant.

Results

The total number of pancreatic operations over the period 1971–1984 was 244, comprising 171 anastomoses (72 per cent) and 69 resections (28 per cent). Over the second interval from 1985 to June 1998, the total number of operations on the pancreas was 303, comprising 263 anastomoses (87 per cent) and 40 resections (13 per cent). There was a greater percentage use of resection in the first

Table 3 Surgical procedures performed in 109 patients with chronic pancreatitis undergoing pancreatic resection

	Total (n=109)	1971–1984 (n=69)	1985–1998 (n=40)
Puestow procedure*	61 (56)	43 (62)	18 (45)‡
Whipple's resection†	43 (39)	21 (30)	22 (55)§
Total pancreatectomy	5 (5)	5 (7)	0 (0)
Total	109 (100)	69 (100)	40 (100)

Values in parentheses are percentages *Left pancreatectomy with splenectomy and pancreaticojejunostomy; associated procedures were carried out in 12 patients, cholecystectomy in 12 and hepaticojejunostomy in five †Since 1996, Longmire–Traverso pylorus-preserving partial pancreaticoduodenectomy. ‡ $P = 0.09$, § $P = 0.01$ versus 1971–1984 (Fisher's test)

observation period than in the second (28 *versus* 13 per cent; $P < 0.0001$). The frequency of use of each type of resection differed between the two intervals (Table 3). Surgery was performed a mean(s.d.) 4.1(3.8) years after the onset of disease. The mean(s.d.) age of patients undergoing resection was significantly lower in the first period (34 (range 14–57) *versus* 51 (range 31–79) years; $P = 0.001$). With the sole

Table 4 Postoperative course in 109 patients with chronic pancreatitis undergoing pancreatic resection

	Total (<i>n</i> = 109)	1971–1984 (<i>n</i> = 69)	1985–1998 (<i>n</i> = 40)
Extra-abdominal complications	10 (9)	8 (12)	2 (5)
Intra-abdominal complications	17 (16)	12 (17)	5 (12)
Fistula	10 (9)	7 (10)	3 (8)
Pancreatic	7 (6)	5 (7)	2 (5)
Other	3 (3)	2 (3)	1 (2)
Abscess	4 (4)	3 (4)	1 (2)
Haemorrhage	3 (3)	2 (3)	1 (2)
Reoperation	8 (7)*	7 (10)	1 (2)
Death	4 (4)	4 (6)	0 (0)

Values in parentheses are percentages *One patient underwent a third operation for haemorrhage 24 h after the second

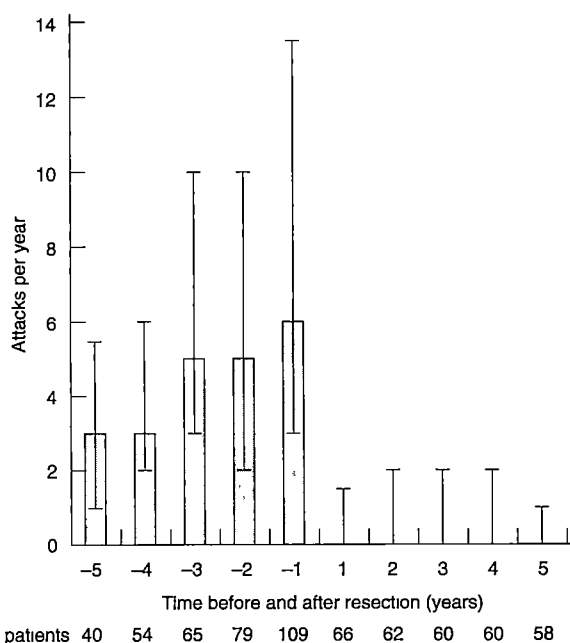


Fig. 1 Trend in pain recurrence over 10 years, from 5 years before to 5 years after operation in patients undergoing pancreatic resection for chronic pancreatitis. Values are median (25–75th percentile)

exception of cystic dystrophy of the duodenal wall, there were no differences in the indications prompting resection.

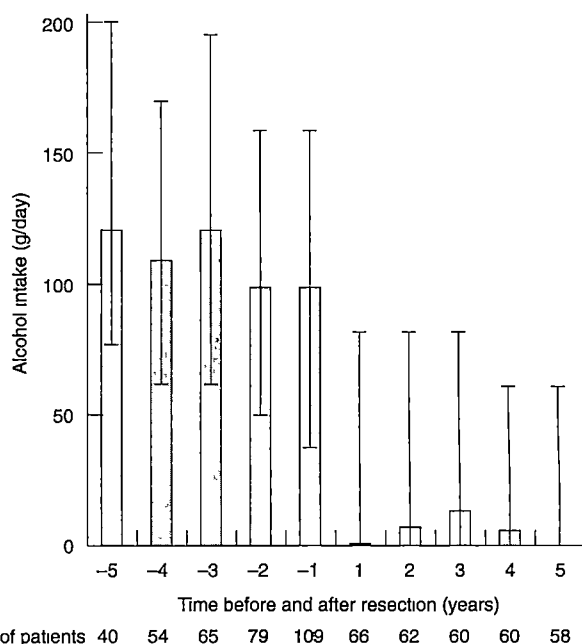


Fig. 2 Trend in alcohol intake over 10 years, from 5 years before to 5 years after operation in patients undergoing pancreatic resection for chronic pancreatitis. Values are median (25–75th percentile)

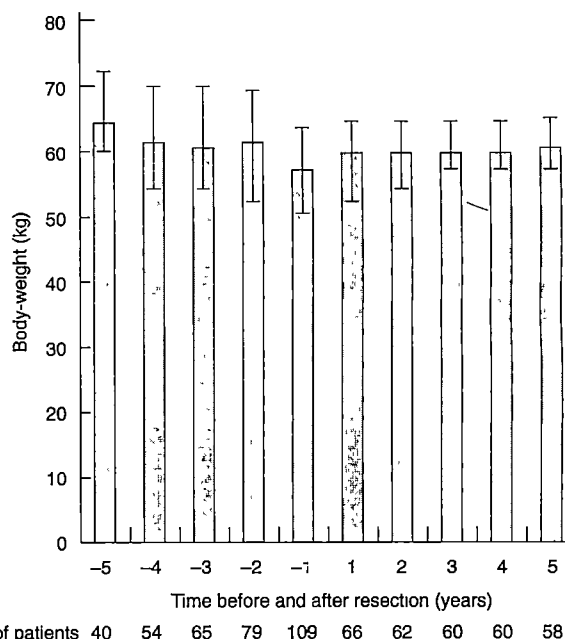


Fig. 3 Trend in body-weight over 10 years, from 5 years before to 5 years after operation in patients undergoing pancreatic resection for chronic pancreatitis. Values are median (25–75th percentile)

The mean(s.d.) duration of the operation decreased in the second period (344(11) *versus* 313(99) min; $P=0.01$), as did the need for units of transfused blood in the course of the operation (4.7(3.6) *versus* 1.2(1.6) units; $P=0.0001$). The mean hospital stay overall was 35 days for total pancreatectomy, 16 days for head resections and 12 days for distal resections. There was a reduction in the second interval from 18 to 14 days in the case of partial pancreaticoduodenectomy and from 12 to 8 days in the case of Puestow resections ($P<0.01$). The mean hospital stay for patients undergoing pylorus-preserving pancreaticoduodenectomy dropped to 11 days.

Table 4 summarizes the morbidity and mortality data for the 109 patients considered. The abdominal complication rate decreased in the second 14-year period (17 *versus* 12 per cent), although the difference was not significant ($P>0.05$). No differences were observed in the types of complications. The perioperative mortality rate was 4 per cent; two patients died from haemorrhagic shock and two from septic shock. All four deaths occurred in first period and the last perioperative death dates back to 1980. In addition to these four patients, a further 35 died in the course of long-term follow-up after a median of 9 (25–75th percentile 4–12; range 1–18) years. The most frequent cause of death was onset of carcinoma (ten patients). All five patients submitted to total pancreatectomy died as a result of decompensated glucose metabolism disorders. The cause of death was unknown in one patient and five other patients died from other causes.

The median follow-up in this series was 10 (25–75th percentile 3–19; range 0–27) years and only one patient dropped out. Exocrine insufficiency has been observed in almost all patients (more than 95 per cent). Endocrine insufficiency is currently present in 72 per cent of the 69 surviving patients. Compensation is achieved with standard dietary measures in three patients, while 12 require oral antidiabetes medication. Thirty-five patients need insulin therapy. Before operation 19 patients (17 per cent) were diabetic; a further 31 patients are currently suffering from this condition. Apart from the five patients who underwent total pancreatectomy, 14 patients developed the disease during the year immediately following surgery.

The pain trend (Fig. 1) showed a progressive, statistically significant increase from year 5 before operation to the year immediately preceding surgery. After resection, a significant decrease was found in both the number of patients experiencing pain and the number of annual pain recurrences ($P<0.003$). Over the 10-year period considered, there was a significant progressive preoperative reduction in both the percentage of drinkers (preoperative year 5, 77 per cent (84 patients); preoperative year 1, 60 per cent (65 patients)) and in the amount of alcohol drunk (preoperative

year 5, 116.2 g/day; preoperative year 1, 76.3 g/day). There was a further significant reduction in alcohol intake after operation ($P<0.001$) (Fig. 2). There were no significant changes in the percentage of smokers or number of cigarettes smoked daily before and after operation (73 per cent (80 patients) *versus* 69 per cent (75 patients); 21 *versus* 18 cigarettes per day). Before operation there was a significant, progressive reduction in body-weight, whereas after operation 65 per cent of patients (71 patients) showed a significant, steady gain in body-weight ($P<0.001$) (Fig. 3).

Discussion

Although the overall number of patients undergoing surgery for chronic pancreatitis increased over the years, a proportional reduction in the number of patients undergoing resection was observed. The series was divided arbitrarily into two 14-year periods and there was a statistically significant decrease in the second interval from 28 to 13 per cent of all operations for chronic pancreatitis. This finding undoubtedly reflects a surgical preference for an anastomotic approach, but is probably also an indication of improved diagnostic capability. Up until 1976, in fact, in the absence of a valid preoperative diagnostic assessment, findings of a 'tumour' at laparotomy prompted the surgeon to perform a resection pending a pathological diagnosis.

Another significant change observed over the years was in the type of resection. Although there were no statistically significant changes over the years in the indications for resection, since pain is still the symptom that most often makes surgical treatment mandatory, more thorough analysis reveals that, in the past few years, new indications have emerged such as cystic dystrophy of the duodenal wall and pancreas divisum. These conditions can be treated by resection of the pancreatic head only after failure of endoscopic treatment, which remains the treatment of choice^{19,21,26–29}. Knowledge of these rare causes, although they are being increasingly detected, led to a progressive and statistically significant increase in the proportion of partial pancreaticoduodenectomies performed in the second 14-year period of this study (30 *versus* 55 per cent). The number of Puestow procedures also diminished over the years, although not significantly. This can mainly be explained by the fact that this procedure is now confined to patients presenting problems of differential diagnosis *versus* intraductal tumours or when having to deal with a sectorial pancreatitis limited to the tail or with a pseudocyst involving the spleen^{6,30,31}. In the second interval, total pancreatectomy was completely abandoned.

The steady increase in expertise of the surgical team accounts for the significant reduction observed over the years in operating times, numbers of blood units transfused

and length of hospital stay. However, no significant differences were observed in morbidity and mortality rates, and no differences were found with regard to long-term results. The pain trend was monitored thoroughly in all patients, and from this standpoint the results reported are comparable to those of other surgical series described in the literature. Only six (10 per cent) of 58 patients observed 5 years after operation showed persistence of pain symptoms, while 90 per cent of patients were pain free. This percentage closely resembles the figure of 86 per cent at 46 months reported by Traverso *et al.*^{32,33} after pylorus-preserving pancreaticoduodenectomy, 79 per cent at 3–7 years described by Büchler *et al.*³⁴ after duodenum-preserving resection of the pancreatic head, and 85 per cent at 5 years reported by Ashley and Reber³⁵ with the classic Whipple procedure.

The duodenum-preserving head resection for chronic pancreatitis introduced by Beger *et al.*³⁶ in 1985 was never performed. This was because the indication for resection of this part of the pancreas is related, in the majority of cases, to chronic pancreatitis secondary to cystic dystrophy of the duodenal wall, in which case preserving the duodenum would leave the aetiological factor in place. Inflammatory masses of substantial diameter in the head are uncommon except in the case of cystic dystrophy. Up until 1995 a Whipple pancreaticoduodenectomy was invariably performed. Since 1996 the operation of choice for resection of the head has been a pylorus-preserving pancreaticoduodenectomy.

In conclusion, the results of this study show that, in the surgical treatment of patients with chronic pancreatitis, the number and type of resections performed has changed somewhat over the years. This is certainly related to a preference, where possible, for an anastomotic approach, but also to advances in knowledge of the rarer causes of the disease that require resection and to improvements in the ability to diagnose them. Resection has proved effective in resolving pain associated with chronic pancreatitis.

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Functional and morphological changes in the pancreatic remnant following pancreaticoduodenectomy with pancreaticogastric anastomosis

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Background: The aim was to evaluate pancreatic exocrine and endocrine function, pancreatic atrophy and main pancreatic duct dilatation in the pancreatic remnant following pancreaticoduodenectomy and pancreaticogastrostomy.

Methods: Nineteen patients who underwent pancreaticoduodenectomy and pancreaticogastrostomy for benign or malignant pancreatic tumours with a histologically normal pancreatic resection margin were studied prospectively. The median interval between operation and evaluation was 32 (range 12–120) months. Pancreatic exocrine insufficiency was assessed by measuring 72-h faecal fat concentrations and faecal-1 elastase. Fasting blood glucose, haemoglobin A1c, serum peptide C and insulin levels were used to assess endocrine function. Pancreatic parenchymal thickness and main pancreatic duct diameter were measured before operation and at evaluation using computed tomography (CT).

Results: Faecal fat excretion was raised in 16 of 17 patients; faecal-1 elastase was reduced in all 17 patients. None of the 17 non-diabetic patients had developed diabetes mellitus at follow-up. A significant decrease in pancreatic parenchymal thickness and increased dilatation of the main pancreatic duct were observed on CT at evaluation ($P = 0.01$ and $P = 0.01$ respectively). Pancreatic atrophy, assessed by subtracting the diameter of the pancreatic duct from the total gland thickness, tended to develop over time, but at the limit of statistical significance ($P = 0.06$).

Conclusion: A median of 3 years following pancreaticoduodenectomy and pancreaticogastrostomy, patients remained free from diabetes but developed marked pancreatic exocrine insufficiency.

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Introduction

Following pancreaticoduodenectomy, gastrointestinal pancreatic drainage can be restored using either a pancreaticojejunal anastomosis (PJA) or pancreaticogastric anastomosis (PGA). The first successful pancreaticogastrostomy was done in 1946¹. Since 1985, pancreatic drainage using PGA has been performed in a number of surgical units. Reasons for using this approach include the proximity of the posterior wall of the stomach to the non-resected pancreas and the excellent blood supply of the stomach. The mortality and morbidity rates related to anastomotic fistula are similar, or perhaps less, than those observed following PJA^{2–5}. These results may be explained

in part by neutralization of pancreatic enzymatic secretions by gastric acid. The long-term outcome of PGA, including the morphological and functional reserves of the remaining body and tail of the pancreas, has yet to be determined.

Pancreaticoduodenectomy entails surgical reduction of approximately 30–50 per cent of pancreatic parenchymal tissue⁶. The islets of Langerhans contain β cells, which are present throughout, but with a predominance in the tail of the pancreas^{7,8}; theoretically they should not be affected and diabetes should not be an inevitable outcome following pancreaticoduodenectomy. Pancreatic exocrine function may be reduced as a sizeable reduction in glandular tissue may decrease pancreatic secretions leading to fat malabsorption. Other mechanisms that may contribute to

malabsorption following this type of surgery include stenosis of the PGA and inactivation of pancreatic enzymes by gastric acid secretion. In this prospective study, a cohort of patients who had pancreaticoduodenectomy and PGA, with a histologically normal remaining pancreas, were examined to determine late development of pancreatic endocrine or exocrine dysfunction. Pancreatic atrophy in the remaining pancreatic parenchyma and main pancreatic duct dilatation was also measured.

Patients and methods

Patients

This study included 19 patients who had previously undergone pancreaticoduodenectomy with PGA at Beaujon Hospital between October 1987 and November 1996. During this interval 143 similar procedures were performed. Patients who had surgery for pancreatic adenocarcinoma or for chronic calcified pancreatitis were excluded owing to the poor survival rates in the former, and difficulties in interpreting pancreatic endocrine and exocrine function in the latter. The 19 patients included in the study comprised 12 women and seven men with a mean age of 55 (range 31–71) years. The remaining patients were either lost to follow-up or refused to participate. The median interval between surgery and evaluation was 32 (range 12–120) months; all patients had a minimum follow-up of 1 year. The indications for pancreatectomy were benign lesions ($n = 14$), including three ampullary tumours, two serous cystadenomas, three neuroendocrine tumours, one neurofibroma and five intraduct papillary mucinous tumours (all of which were localized without features of malignant transformation), or malignant lesions ($n = 5$), including three ampullary adenocarcinomas, one duodenal adenocarcinoma and one cholangiocarcinoma. Histology of the pancreatic resection margin was normal in all patients with malignancy and the pancreatic remnant was macroscopically normal without evidence of obstructive pancreatitis.

The operative procedure included antrectomy and an end-to-side one-layer pancreaticogastrostomy between the posterior wall of the stomach and the resected pancreatic surface using non-absorbable sutures (*Fig. 1*). The pancreatic parenchyma was sutured to the seromuscular layer of the gastric wall with no attempt to perform a mucosa-to-mucosa anastomosis. A stent was used peroperatively only to avoid pancreatic duct stenosis during the suturing technique and was removed through the gastric lumen before completion of the gastrojejunal anastomosis. Finally, a cholecystectomy was followed by an end-to-side hepaticojejunum anastomosis on the first jejunal loop, 20–50 cm proximal to the gastrojejunal anastomosis.

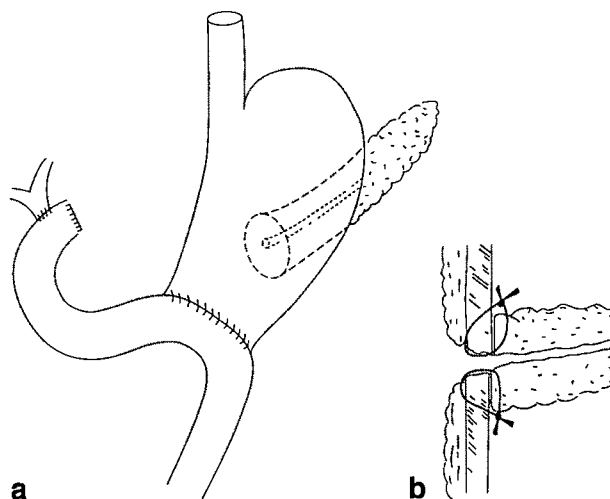


Fig. 1 Technique of pancreaticoduodenectomy with pancreaticogastric anastomosis.

a The neck of the pancreas is anastomosed to the posterior wall of the stomach in an end-to-side fashion.

b Detail of the suturing technique of the pancreaticogastric anastomosis is shown, revealing direct suture of the pancreatic parenchyma to the seromuscular layer of the stomach

There were no perioperative deaths. Surgery was complicated by anastomotic fistula in two patients, both of whom were successfully treated conservatively.

Evaluation of pancreatic exocrine function

Steatorrhoea was assessed by measuring faecal fat excretion as a mean of 72 h (normal 2–6 g per 24 h) and faecal-1 elastase (normal 200–500 µg per g stool). Stool specimens were collected over 3 consecutive days with the patient on a high-fat diet (50 g of butter). Pancreatic enzyme supplements were discontinued before specimen collection. Faecal-1 elastase was measured by enzyme-linked immunosorbent assay. A value of less than 200 µg per g stool was taken as an indirect diagnosis of pancreatic insufficiency^{9–11}. This method remains the investigation of choice in the diagnosis and quantification of fat malabsorption¹². To overcome the possibility of inactivation of pancreatic enzymes owing to the low pH of gastric juice, faecal fat concentrations and faecal-1 elastase measurements were also performed in three patients treated with omeprazole 20 mg twice daily for 8 days. Stool analyses were performed in one centre to avoid interlaboratory variations.

Evaluation of pancreatic endocrine function

The presence of diabetes was sought from analysis of fasting blood glucose (normal less than 7 mmol/l), fasting serum insulin level (normal less than 15.6 units/l), fasting serum

peptide C (normal less than 3.2 ng/ml) and glycosylated haemoglobin A1c (normal 4.6–5.6 per cent). Diabetes was defined, in accordance with the American Diabetes Association, as a fasting blood glucose concentration of greater than 7 mmol/l^{13–15}. A fasting blood glucose level between 5.56 and 7 mmol/l was defined as glucose intolerance, according to this new classification¹⁴.

Morphological assessment of residual pancreas

Examination of the remaining pancreas following pancreaticoduodenectomy was performed using computed tomography (CT). Five-millimetre consecutive sections were imaged before and after contrast injection, in the presence of upper digestive contrast opacification. Each scan was compared with the pancreatic scan obtained before operation, unless acute pancreatitis, pseudocyst or dilatation of the main pancreatic duct was present. Analysis was done by the same experienced radiologist. The thickness of the pancreas (including the main pancreatic duct) and the diameter of the main pancreatic duct (measured perpendicular to the axis of the pancreas) were measured at 2 and 4 cm from the extremity of the caudal portion of the pancreas. Measurements were performed at two separate sites to limit artefactual variations at the level of the surgical anastomosis (e.g. folding of the stomach wall or distortion of the pancreas). The main pancreatic duct was considered dilated if the diameter exceeded 3 mm at 4 cm from the caudal extremity of the pancreas (pancreatic body) or was greater than 2 mm at 2 cm from the caudal extremity (pancreatic tail)¹⁶. When the main pancreatic duct was not visualized, its diameter was estimated as 1 mm in order to permit evaluation of the pancreatic parenchymal thickness. Parenchymal thickness was calculated by subtracting the pancreatic duct diameter from the total gland thickness for each individual patient at 2 and 4 cm from the caudal extremity of the pancreas. The presence of pseudocysts, calcification and/or fatty infiltration (hypodensity) in the pancreas was also noted.

Statistical analysis

An analysis between matched variables was performed using the paired Student's *t* test and a logistic regression test was used for assessing the correlation of parenchymal atrophy with time. *P* < 0.05 was considered statistically significant.

Results

Pancreatic exocrine function (Table 1)

In the 6 months following pancreaticoduodenectomy and PGA, 11 of 19 patients received enteric-coated pancreatic

enzyme supplements because of diarrhoea. Pancreatic enzyme supplements were discontinued before stool collection in all patients. Faecal fat excretion was analysed in 17 patients (one patient refused to have stools collected and another had incomplete collection). Faecal fat excretion was increased in 16 patients with a median concentration of 28 g per 24 h. The faecal fat concentration was greater than 10 per cent in all patients. Faecal-1 elastase concentrations were decreased in all 17 patients analysed, with a median concentration of 12 µg per g stool. Compared with preoperative values, patients had a mean decrease in weight of 6 kg at follow-up. In the three patients who were re-evaluated during treatment with a proton pump inhibitor, faecal fat excretion and concentrations remained raised and faecal-1 elastase concentrations were low (data not shown). One of these patients was receiving pancreatic enzyme supplements when analysed.

Pancreatic endocrine function

Results of fasting glucose estimation were normal for 17 of 19 patients in the month before operation; none became diabetic as a result of surgery. Glucose intolerance, however, was identified in three patients during follow-up, after 42, 73 and 120 months. Two patients with non-insulin-dependent diabetes before operation became insulin dependent following surgery.

Pancreatic morphology

CT evaluation was not possible in one of the two patients who developed a postoperative fistula because of a persisting anastomotic pseudocyst. Pancreatic calcification or pseudocyst was absent in the remaining 18 patients. An area of fatty infiltration was noted in two patients with hypodense features on CT. The main pancreatic duct was found to be dilated at 4 and 2 cm from the caudal extremity of the pancreas (*P* = 0.02 and *P* = 0.01 respectively). When pancreatic parenchymal thickness alone was measured, a significant decrease was found after operation (*P* = 0.000001 and *P* = 0.001 at 2 and 4 cm respectively; Table 2). A tendency for the thickness of the pancreatic parenchyma

Table 1 Pancreatic exocrine function following pancreaticoduodenectomy and pancreaticogastric anastomosis in 17 patients

	After operation (<i>n</i> = 17)	Normal range
Faecal fat excretion (g per 24 h)	28 (17–115)	2–6
Faecal-1 elastase (µg per g stool)*	12 (1–134)	200–500
Faecal fat concentration (%)	54 (20–84)	< 10

Values are median (range). **n* = 16

Table 2 Pancreatic parenchymal thickness at 2 cm from the caudal extremity of pancreas before operation and at evaluation

Patient no.	Parenchymal thickness (mm)*	
	Before operation	At evaluation
1	16	7
2	15	16
3	18	13
4	12	10
5	18	10
6	15	13
7	15	13
8	20	15
9	16	7
10	21	15
11	16	15
12	15	12
13	18	16
14	11	11
15	19	11
16	20	18
17	13	10
18	17	10

Pancreatic parenchymal thickness was calculated as pancreatic thickness minus pancreatic duct diameter. Changes in parenchymal thickness were significant ($P < 0.000001$) *Paired Student's *t* test

to decrease over time was also noted, but at the limit of statistical significance ($P = 0.06$). The reduction in parenchymal thickness was estimated to be 0.8 mm per year. There was no significant dilatation of the main pancreatic duct over time.

Discussion

This study included only patients with benign pancreatic disease (excluding chronic pancreatitis) or a localized malignant lesion who had pancreaticoduodenectomy and PGA. Pancreatic exocrine insufficiency, as demonstrated by increased faecal fat excretion, was found in 16 of 17 patients at a median of 32 months after operation. In addition, all patients evaluated had an abnormally low level of faecal-1 elastase. The latter test allows indirect diagnosis of pancreatic exocrine dysfunction with a sensitivity and specificity of 93 and 93 per cent respectively⁹⁻¹¹. Faecal-1 elastase levels correlated well with faecal fat excretion, confirming results obtained in previous studies. Fat malabsorption usually developed in the first year following surgery and may be explained by several mechanisms: inactivation of pancreatic enzymes as a result of low gastric pH, stenosis at the pancreatic ductal-gastric anastomosis, and/or pancreatic atrophy secondary to anastomotic stenosis or abnormalities of neurohormonal stimulating factors.

An influence of gastric acidity on pancreatic enzyme activity has been suggested previously¹⁷. Takada *et al.*¹⁸ demonstrated irreversible inactivation of pancreatic amylase and lipase at gastric pH levels of less than 3.0 following pancreaticoduodenectomy and PGA. At pH levels above 3.0, pancreatic enzyme activity progressively increased in proportion to the increase in gastric pH. At a pH above 5.0, amylase and lipase activities were estimated to be greater than 70 and 75 per cent respectively¹⁸. Pancreatic secretions were isolated in gastric contents over 3 years after operation suggesting patency of the PGA. However, analysis of three patients who received proton pump inhibitors in the present study failed to record any modification in either faecal fat excretion or faecal-1 elastase.

Whether pancreatic exocrine insufficiency occurs more frequently after pancreaticoduodenectomy and PGA compared with PJA is not known as no direct comparison has yet been performed. Pancreatic exocrine dysfunction was described in a study of 14 patients who had pancreaticoduodenectomy and PJA for an ampullary tumour¹⁹ using a para-aminobenzoic acid/para-aminosalicylic acid test. However, no evaluation was made with regard to pancreatic endocrine function or morphological changes. Use of pancreatic supplements in the present study (11 of 19 patients) was similar to that previously reported²⁰.

Pancreaticoduodenectomy and PGA did not predispose to the development of diabetes. Andersen *et al.*²⁰ similarly reported only two patients with diabetes following pancreaticoduodenectomy in 58 patients analysed; however, the method of detecting diabetes was not defined. Using stringent diagnostic criteria in the present study, only two patients with pre-existing non-insulin-dependent diabetes became insulin dependent following surgery. Although four patients were followed for over 5 years in the present study and all had normal pancreatic endocrine function, no conclusions can be made regarding the possibility of developing diabetes much later.

Morphological changes were clearly demonstrated by CT. Both progressive reduction in pancreatic parenchymal thickness over time and an increase in the main pancreatic duct diameter were observed. Pancreatic duct dilatation is difficult to explain in the absence of direct visualization of the PGA. Dilatation may occur secondary to stenosis of the anastomosis or result from involution of the gland parenchyma. The only study evaluating patency of pancreaticogastric anastomoses was performed by Arnaud *et al.*²¹. Retrograde pancreatography performed 3 months after pancreaticoduodenectomy demonstrated a patent anastomosis in nine patients. However, these results cannot be extrapolated to longer follow-up. Obstruction at the anastomosis may be related to lack of mucosal apposition, which is not feasible owing to the thin calibre of the

pancreatic duct; anastomotic patency was not examined in the present study. Involution of pancreatic tissue may also occur without anastomotic stenosis following disruption of the pancreatic neurohormonal stimulating mechanisms resulting from pancreaticoduodenectomy. In addition, negative feedback following a high-caloric jejunal load may result in reduced exocrine secretion²².

No correlation was observed between either reduced pancreatic exocrine function or CT-documented pancreatic atrophy and the development of insulin-dependent diabetes. This confirms the results of previous studies that examined pancreatic endocrine function following pancreaticoduodenectomy and occlusion of the non-anastomosed main pancreatic duct using neoprene injection²³.

In summary, at a median of 3 years following surgery, patients who had pancreaticoduodenectomy with a PGA developed marked pancreatic exocrine insufficiency but remained free from diabetes.

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Bacterial translocation in patients undergoing abdominal aortic aneurysm repair

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Background: Bacterial translocation occurs in humans and is associated with an increased incidence of septic morbidity. The aims of this study were to determine the prevalence of bacterial translocation in patients undergoing open abdominal aortic aneurysm (AAA) repair and to identify any association with postoperative septic complications.

Methods: This was a prospective observational study in which patients undergoing aneurysm repair were assessed for evidence of bacterial translocation by culture of a mesenteric lymph node (MLN), small bowel serosal exudate and thrombus within the aneurysm. All postoperative septic complications were recorded.

Results: A total of 51 patients was studied (40 men, 11 women; median age 72 years). Enteric bacteria were isolated from the MLNs of five patients (prevalence of bacterial translocation 10 per cent), one of whom also yielded growth from the serosal exudate. Septic morbidity occurred in four of five patients in whom bacterial translocation was identified, compared with nine of 46 in those without translocation ($P=0.013$, Fisher's exact test, mid P). One patient in whom *Escherichia coli* was grown from the MLN developed an aortoenteric fistula, with a coliform species isolated from the graft.

Conclusion: This study suggests that bacterial translocation occurs in patients undergoing AAA repair. It is associated with an increased incidence of postoperative septic morbidity and provides a possible mechanism for infection of prosthetic aortic grafts.

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Introduction

Bacterial translocation is defined as the passage of gastrointestinal microflora across the lamina propria to local mesenteric lymph nodes (MLNs), and from there to distant sites. Bacterial translocation is known to occur in humans and has been shown to be associated with a significantly higher incidence of postoperative septic morbidity in patients undergoing laparotomy^{1,2}. It has also been implicated as a possible factor in the pathogenesis of multiple organ failure³, although a causal relationship has yet to be proved⁴.

Prosthetic aortic graft infection is an uncommon but serious complication of abdominal aortic aneurysm (AAA) surgery, with a reported incidence of between 1 and 6 per cent and a mortality rate of up to 77 per cent^{5–9}. Historically, most graft infections have been attributed to skin commensals such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, presumably as a result of contam-

ination of the graft at the time of operation¹⁰. Recent evidence suggests that many graft infections may be caused by Gram-negative enteric bacteria, such as *Escherichia coli*¹¹.

The aim of this study was to identify whether bacterial translocation occurs in patients undergoing open repair of an AAA and to establish whether the occurrence of this phenomenon predisposes to postoperative septic complications.

Patients and methods

This was a prospective observational study conducted with ethics committee approval. A consecutive series of patients undergoing open repair of an AAA was studied. Patients were excluded if sampling of tissues was considered clinically inappropriate at the time of operation, such as in patients with rupture, for whom the priority was proximal control of the aneurysm. Immediately after opening the abdomen and before administration of prophylactic anti-

biotics, tissue sampling was performed to identify the presence of bacterial translocation. This included excision of a lymph node from the ileocolic mesentery using a fresh surgical blade and collection of serosal exudate in a polythene bag into which the small bowel was packed for the duration of the operation. In addition, a sample of mural thrombus was obtained after opening the aneurysm sac. The MLN and thrombus were placed in sterile saline, and all samples were transported promptly to the microbiology department for analysis. The bacteriological methods used have been described elsewhere¹.

The antibiotic prophylaxis used for the first 20 patients was co-amoxiclav 1.2 g intravenously, followed by cefuroxime 1.5 g and metronidazole 500 mg intravenously for the remainder. The administration of antibiotics was withheld until the MLN had been harvested. Antibiotics were usually prescribed for a further 24–48 h.

All patients were closely monitored after operation for septic complications. These were defined as clinical, radiological or haematological evidence of infection in the presence of positive bacterial cultures from appropriate specimens.

Results

A total of 51 patients was entered into the study (40 men, 11 women; median age 72 (interquartile range 66–77) years). All but two patients had elective operations. A MLN was taken for culture in all patients. Positive growth of an indigenous enteric species was observed in five patients (prevalence of bacterial translocation 10 per cent). Three organisms were isolated in one patient and single organisms in the other four (*Table 1*). There were no differences in terms of clinical condition or co-morbidity between patients with positive evidence of bacterial translocation and those with a negative MLN.

A sample of serosal exudate was obtained from 45 patients. Growth of an enteric species (*Proteus mirabilis*) was obtained in only one patient. This occurred in a patient in whom *Enterococcus faecalis* was cultured from the MLN. A scraping of mural thrombus was submitted for analysis in 25 patients, but none produced positive bacterial growth.

A total of 16 septic complications occurred after operation in 13 patients: chest infection (eight patients), urinary infection (four), wound infection (one), central line infection (one), septicaemia (one) and graft infection (one). The overall incidence was 25 per cent. *Table 2* shows the causative organisms isolated from the infections; 12 were enteric in nature. Of four patients with a positive MLN who subsequently developed a septic complication, three grew the same bacterium from both sites (two *E. coli* and one

Table 1 Bacteria cultured from mesenteric lymph nodes (*n* = 5)

Patient no.	Bacterial species isolated
1	<i>Escherichia coli</i> <i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i>
2	<i>Escherichia coli</i>
3	<i>Escherichia coli</i>
4	<i>Proteus mirabilis</i>
5	<i>Enterococcus faecalis</i>

Table 2 Nature of bacteria responsible for septic complications

Bacterial species	No. of isolates
Enteric (<i>n</i> = 12)	
Coliforms	5
<i>Escherichia coli</i>	3
<i>Proteus mirabilis</i>	2
<i>Citrobacter</i> spp.	1
<i>Klebsiella</i> spp.	1
Non-enteric (<i>n</i> = 5)	
<i>Pseudomonas aeruginosa</i>	2
<i>Haemophilus influenzae</i>	1
<i>Staphylococcus aureus</i>	1
<i>Streptococcus</i> spp.	1

P. mirabilis). The incidence of septic morbidity in the patients in whom viable micro-organisms were cultured from the MLN was four of five, compared with nine of 46 in those with no growth ($P = 0.013$, Fisher's exact test, mid P).

One of the patients in whom *E. coli* was cultured from the MLN made an uneventful postoperative recovery, but subsequently presented 2.5 years later with an aortoenteric fistula. He underwent an extra-anatomic bypass and excision of the graft. Culture of the graft grew a lactose-fermenting coliform species. Although this organism was not identified further, its antibiotic sensitivity profile was identical to that of the *E. coli* isolated from the MLN at the original operation. No graft sepsis has been identified in any of the other patients to date.

Discussion

This study provides evidence that bacterial translocation occurs in some patients undergoing open AAA repair and that its occurrence is associated with an increased incidence of postoperative septic morbidity.

Bacterial translocation was originally identified in animal studies, but has since been shown to occur in humans^{1,2}. In a large prospective study of patients undergoing laparotomy

for a wide range of surgical conditions, bacterial translocation, as assessed by culture of a MLN, was identified in 69 of 448 patients (prevalence 15.4 per cent)². The majority of organisms isolated were indigenous enteric bacteria, most commonly *E. coli*. The presence of bacterial translocation was associated with a significantly higher incidence of postoperative septic morbidity (45 *versus* 19 per cent), similar to that in the present study.

Bacterial translocation may be a normal 'epiphenomenon', occurring in healthy individuals¹². Under normal circumstances the organisms are dealt with by local immune mechanisms. However, in susceptible individuals these mechanisms may fail, permitting egress of translocating bacteria to distant sites via the gastrointestinal lymphatics and systemic circulation, thus potentiating the development of distant sepsis¹². Three patients in the present study grew the same organism in the MLN at the time of operation and from a postoperative septic focus.

The development of an aortoenteric fistula in one of the patients in whom positive growth was obtained from the MLN leads to consideration of the interesting possibility that bacterial translocation is a cause of prosthetic aortic graft infection. Most graft infections are thought to arise as a result of contamination by skin commensals at the time of implantation¹⁰, but other possible causes include transection of contaminated lymphatics, direct extension from an adjacent wound infection, or haematogenous seeding of the graft. In a recent review¹¹ it was observed that just over half the infected grafts grew enteric bacteria, with *E. coli* identified in 12 of 50 patients.

If patients in whom bacterial translocation is demonstrated are at an increased risk of developing late graft sepsis, what therapeutic options are available? An obvious answer would be to use prolonged antibiotic prophylaxis in an attempt to reduce the risk of infection, but this unfortunately carries the risk of selecting resistant strains of bacteria and *Clostridium difficile*-associated diarrhoea.

Several studies have investigated the significance of contaminated mural thrombus as a potential cause of graft sepsis. The reported prevalence varies widely, between 5 and 37 per cent¹³⁻¹⁵. Each of these studies concluded that the presence of bacteria in intraluminal thrombus does not appear to be an important factor in the development of later graft infection. Not one of the thrombus samples obtained in the present study yielded bacterial growth.

In the present study, the serosal exudate was transported to the microbiology laboratory in a plain specimen bottle for the initial 35 patients. This failed to yield any bacterial growth. After consultation with microbiology colleagues, samples of exudate were placed in aerobic and anaerobic blood culture bottles for the final ten patients. A single enteric species of bacteria was cultured from exudate

transported in this way. This low yield may be due to the fact that antibiotics had already been given, or possibly to a dilutional effect.

This study has demonstrated that bacterial translocation occurs in patients undergoing surgery for an AAA, and that it is associated with an increased incidence of postoperative septic morbidity. It is speculated that this phenomenon may be a cause of late graft sepsis. Demonstration of bacterial translocation at the time of operation may justify prolonged antibiotic therapy. Proving a causal relationship between bacterial translocation and infection will inevitably be difficult, given the relatively low prevalence of demonstrable bacterial translocation and the low incidence of prosthetic aortic graft infection.

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Comparison of cognitive function and quality of life after endovascular or conventional aortic aneurysm repair

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Introduction: The long-term effects of endovascular aortic aneurysm repair on cognitive function and quality of life are not known.

Methods: The cognitive function and quality of life of 82 patients undergoing aortic aneurysm repair (34 endovascular and 48 conventional procedures) were assessed before and 6 months after operation. Cognitive function was quantified using a battery of psychometric tests. Quality of life was assessed with the Medical Outcomes Short Form 36 (SF-36) questionnaire.

Results: Data at 6 months were available for 78 per cent of patients. As a group the patients showed a significant decline on one cognitive function test (visual search) and on two domains of the SF-36 (physical function and vitality) when they were reassessed. There were no significant differences between patients undergoing endovascular or conventional aneurysm repair after 6 months in cognitive function or quality of life.

Conclusion: Endovascular aneurysm surgery had a similar impact on health-related quality of life and cognitive function compared with conventional aneurysm repair. Patients in both groups demonstrated a significant decline in cognitive function.

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Introduction

Evidence-based medicine favours the use of the best available information when deciding on the most appropriate treatment for a particular condition^{1,2}. However, the evidence may be limited or flawed when new treatments are introduced³. In recent years, endovascular aortic aneurysm repair has been introduced worldwide as an alternative to conventional open repair. Endovascular repair may confer significant advantages with respect to length of stay in intensive care, duration of hospitalization and speed of recovery^{4–7}. However, in contrast to conventional surgery, endovascular aortic surgery may be complicated by endoleaks or graft malfunction in up to 20 per cent of patients⁸. The long-term durability of aortic endografts is unproven.

Several studies have reported that patients undergoing conventional aneurysm surgery have retained or improved their quality of life (QoL)^{9–11}. There have been no studies that examined the impact of aneurysm repair on cognitive function. There is evidence that surgery, general anaes-

thetic and even a stay in intensive care can affect cognitive function^{12–15}. Patients undergoing conventional aneurysm repair may spend longer in intensive care than patients having endovascular surgery, which may affect cognitive function. This study attempted to quantify changes in QoL and cognitive function in patients undergoing conventional or endovascular aneurysm repair.

Patients and methods

Eighty-two patients who had infrarenal abdominal aortic aneurysm repair in one surgical centre were studied prospectively to examine changes in health-related QoL and cognitive function. Thirty-four patients had an endovascular procedure (mean age 73 (range 59–82) years) and 48 patients had conventional surgery (mean age 73 (range 59–86) years). These patients were a consecutive series who underwent operation during the same time interval. The indications and technique for both conventional and endovascular aneurysm repair have been detailed elsewhere^{16–19}. The endovascular aortoiliac grafts were

Table 1 Graft configuration, mortality and duration of stay in patients undergoing aortic aneurysm repair

	Endovascular (<i>n</i> =34)	Conventional (<i>n</i> =48)
Graft configuration	30 aortouni-iliac 3 bifurcated 1 tube	32 tube 16 bifurcated
Technical failure	3 (2 conversions)	0
30-day mortality	3	2
Duration of critical care (days)	1 (0–14)	2 (1–21)*
Length of hospital stay (days)	9 (5–44)	12 (7–41)†

Values are median (range) **P* = 0.032, †*P* = 0.053 (Mann–Whitney *U* test)

custom-built in Leicester, the bifurcated prostheses included two Vanguard devices (Boston Scientific, St Albans, UK) and one EVT graft (Endovascular Technologies, Menlo Park, California, UK). The straight prosthesis was a Bard (Bard/Impira, Billerica, Massachusetts, USA) device (Table 1).

Cognitive function and QoL were assessed before operation and again 6 months afterwards. The preoperative assessment was carried out either on the day patients were admitted to hospital or several weeks earlier when they attended a preoperative assessment. All assessments were carried out by a psychologist (A.J.L.). Follow-up assessments were conducted either at the hospital or at the patient's own home.

Cognitive function

The battery of cognitive function tests was designed to assess different areas of cognitive function. Patients completed the Mini Mental State Examination (MMSE)²⁰ in order to obtain a global picture of their cognitive function. Two subtests from the Test of Everyday Attention²¹ were used to assess visual attention and visual search (Map Search and Visual Elevator). Picture naming has been shown to be a sensitive early indicator of dementia²². This was tested using the Howard syllable-length naming test. Finally, episodic memory was assessed by means of the prose recall task from the Rivermead Behavioural Memory Battery²³. This test examines immediate and delayed recall. Parallel forms of all tests were used at the 6-month follow-up assessment, except for the MMSE and the Howard naming test.

Quality of life

QoL was assessed using the Medical Outcomes Short Form 36 (SF-36)²⁴. The SF-36 has been widely used to measure

the impact of many different health interventions. The psychometric properties of the questionnaire are well understood²⁵ and a UK version, which has been fully validated, is available. The form is scored on eight dimensions, which encompass general health, physical function, vitality, bodily pain, social function and mental health. Two dimensions attempt to measure role function (physical and mental), which is related to how health affects the ability to work.

Statistical analysis

Data are presented as median (95 per cent confidence interval). Analysis was performed with non-parametric statistics; paired data were compared with the Wilcoxon signed rank test and unpaired data with the Mann–Whitney *U* test.

Results

Data were available for 64 (78 per cent) of the 82 patients at the 6-month follow-up. Eleven patients had died (endovascular, six; surgical, five); the other seven refused to attend (endovascular, four; surgical, three). Twelve patients completed only the QoL assessment. The operative outcome details of the patient groups are given in Table 1.

Cognitive function

The mean scores for all of the patients from the cognitive test battery before and 6 months after operation are displayed in Table 2. At 6 months patients were significantly

Table 2 Scores from the cognitive function battery for all patients before operation and 6 months after aneurysm repair

	Preoperative	6 months postoperative
MMSE	28 (27–29)	27 (26–28)
Visual search		
Task 1	24 (21–27)	20 (18–22)*
Task 2	43 (39–47)	37 (33–41)*
Visual attention		
Task 1	7 (6–8)	8 (7–9)
Task 2	5 (4–5)	5 (4–5)
Immediate recall	5 (4–6)	6 (5–7)
Delayed recall	3 (2–4)	5 (4–6)
Naming	38 (37–39)	38 (37–39)

Values are median (95 per cent confidence interval). MMSE, Mini Mental State Examination. **P* < 0.05 (Wilcoxon signed rank test)

Table 3 Scores from the cognitive function battery for endovascular and conventional surgical groups before and 6 months after operation

	Endovascular group		Conventional group	
	Preoperative	Postoperative	Preoperative	Postoperative
MMSE	28 (27–29)	28 (27–29)	27 (26–28)	27 (26–28)
Visual search				
Task 1	20.5 (16.6–24.4)	19.0 (15.8–22.2)	24.5 (21.3–27.7)	20.5 (17.0–24.0)
Task 2	41.5 (34.8–48.2)	36.0 (29.7–42.3)	43.5 (38.0–49.0)	37.5 (31.9–43.1)
Visual attention				
Task 1	8 (7–9)	9 (8–10)	6 (5–7)	7 (6–8)
Task 2	4.6 (3.7–5.5)	4.5 (3.9–5.1)	5.3 (4.7–5.9)	4.7 (4.3–5.1)
Immediate recall	4.5 (3.4–5.6)	7.0 (6.0–8.0)	5.0 (3.9–6.1)	5.5 (4.3–6.7)
Delayed recall	2.5 (1.6–3.4)	5.0 (4.1–5.9)	3.5 (2.3–4.7)	4.3 (3.2–5.4)
Naming	38 (37–39)	38 (37–39)	38 (37–39)	38 (37–39)

Values are median (95 per cent confidence interval) MMSE, Mini Mental State Examination. There were no significant differences between the groups

Table 4 Scores from the Medical Outcomes Short Form 36 (SF-36) before and 6 months after operation

	Preoperative	6 months postoperative		P*
		Conventional	Endovascular	
General health	67 (62–72)	70 (64–76)	57 (50–64)	0.15
Physical function	80 (73–87)	55 (47–63)	55 (43–67)	0.84
Vitality	65 (61–69)	60 (55–65)	55 (48–62)	0.84
Bodily pain	74 (67–81)	73 (64–82)	60 (48–72)	0.07
Social function	88 (81–94)	90 (82–98)	90 (80–100)	1.0
Mental health	84 (81–87)	84 (78–90)	84 (78–90)	0.54
Role function				
Physical	50 (40–60)	50 (37–63)	50 (33–67)	0.63
Mental	100 (91–109)	100 (86–114)	67 (52–82)	0.89

Values are median (95 per cent confidence interval). *Mann–Whitney U test

worse overall on the visual search task (task 1, $Z = -2.15$, $P = 0.03$; task 2, $Z = -2.63$, $P = 0.008$).

There was, however, no difference in cognitive function between the endovascular and surgical groups at 6 months (Table 3).

Quality of life

The raw data from the SF-36 were transformed into standard scores from 0 to 100, with high scores indicating better QoL²⁴. There were no significant differences between the SF-36 scores in patients in the endovascular and surgical groups before the operation. For simplicity, the preoperative data have been collapsed across the two groups to compare with outcome at 6 months (Table 4).

First, the effects of aneurysm repair on QoL were examined without discriminating between the endovascular

and conventional surgical patients. The postoperative scores were compared with the baseline scores using paired analysis. This indicated that there was a significant deterioration in the domains of physical function ($Z = -3.33$, $P = 0.001$) and vitality ($Z = -2.16$, $P = 0.03$).

Second, the postoperative scores from the endovascular and conventional aneurysm groups were compared. The endovascular group scored lower on the bodily pain scale at 6 months, a difference that was marginally non-significant ($Z = -1.77$, $P = 0.07$). The two groups were not significantly different in any of the other dimensions.

Discussion

This study examined changes in QoL and cognitive function in patients undergoing endovascular and conventional abdominal aortic aneurysm repair. The analysis revealed that patients undergoing aneurysm surgery, regardless of the procedure, experienced deterioration in QoL after the operation. Overall, patients reported significant deterioration in physical function and vitality 6 months after operation. There was also a significant decline in cognitive function after operation in both groups (especially in visual search tasks). It should be noted, however, that the study did not include an age-matched control group. The deterioration in cognitive function could simply be the result of ageing.

QoL following elective aneurysm surgery has been investigated previously, with similar results to the present study. Perkins *et al.*¹⁰ demonstrated that patients who had conventional aneurysm surgery experienced worsened social function 6 weeks after the procedure, whereas mental health and physical role limitation improved in all postoperative analyses. Magee *et al.*⁹ reported that patients

retained excellent QoL following elective transperitoneal aneurysm repair.

The impact of endovascular aneurysm repair on QoL has attracted recent attention. The 'minimally invasive' nature of the operation might be expected to translate into improved QoL. However, patients undergoing endovascular aneurysm repair need to undergo a programme of postoperative surveillance to identify aortic dilatation, graft failure or the development of endoleaks²⁶. Additionally, failure of aneurysm regression or the development of an endoleak may necessitate intensive investigation and further endovascular or conventional aortic surgery. It might be surmised that these factors would adversely influence QoL.

Surprisingly, the present study demonstrated similar QoL scores both before and after operation in patients undergoing conventional and endovascular aneurysm repair. The endovascular cohort reported more pain at the 6-month follow-up, which may be related to a persistence of claudication in some patients, and ongoing treatment for persistent endoleaks²⁷. It is possible that QoL could still improve after 6 months, but evidence from the literature suggests that there is little recovery after the initial postoperative phase¹⁰. The findings of the present study confirm preliminary data presented by two other groups. Fillinger *et al.*²⁸ used the SF-36 to study 37 patients undergoing endovascular or conventional aneurysm surgery. They revealed improved functional outcome for the endovascular patients 1 month after operation, but identical QoL scores for the two groups at 6-month review. Similarly, Malina *et al.*²⁹ reported no significant differences in QoL scores (using the Nottingham Health Profile) in 33 patients 3 months after endovascular or conventional aneurysm repair.

The results from the present study have suggested that the decision to offer endovascular aneurysm repair should not be made on the expectation of improved QoL or cognitive function. However, the study was cohort based and not randomized. The 6-month mortality rate after endovascular repair was 18 per cent (six of 34 patients). The patients were high risk and many were not suitable for conventional surgery. Further data should emerge regarding mortality, morbidity and the impact on QoL from the forthcoming National Health Service Research and Development sponsored prospective randomized trials of endovascular aneurysm repair (EVAR) *versus* best medical therapy (EVAR II trial) or conventional surgery (EVAR I trial).

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Aminoguanidine attenuates endotoxin-induced mesenteric vascular hyporeactivity

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Background: The aim of this study was to investigate the effects of inducible nitric oxide synthase inhibition by aminoguanidine on endotoxin-induced reduction in mesenteric blood flow.

Methods: Twenty Sprague-Dawley rats (180–230 g) allocated into four groups were administered either *Escherichia coli* endotoxin 1 mg/kg intraperitoneally or its solvent saline and were pretreated with either aminoguanidine (15 mg/kg intraperitoneally 20 min before and 2 h after endotoxin injection) or saline. Some 4 h after endotoxin injection, animals were anaesthetized, arterial blood pressure and mesenteric blood flow were measured and the resistance in the mesenteric vascular beds was then calculated. The effect of phenylephrine (1–30 µg/kg intravenously) on these parameters was also investigated.

Results: Endotoxin did not significantly modify the mean arterial blood pressure but decreased mesenteric blood flow, by increasing the vascular resistance (mean(s.e.m.) 7.8(1.0) versus 13.7(1.2) mmHg per min per ml for control versus endotoxin groups; $n = 5$, $P = 0.0099$). Aminoguanidine alone had no effect on either the mean arterial blood pressure or mesenteric blood flow, but it completely blocked the effects of endotoxin. On the other hand, endotoxin significantly attenuated the responsiveness to phenylephrine which was restored by aminoguanidine.

Conclusion: The present results indicate that endotoxin decreases the mesenteric vascular blood flow by increasing vascular resistance and decreases responsiveness to phenylephrine. The effects of endotoxin were inhibited by aminoguanidine. The mesenteric vasoconstriction in response to endotoxin might not be explained by the overproduction of nitric oxide; other actions of aminoguanidine may explain its inhibitory effect.

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Introduction

Circulatory failure in septic shock is characterized by systemic vasodilatation, diminished blood flow to various vascular beds¹ and hyporesponsiveness to vasoconstrictors². Despite some opposing views^{3,4} there is strong evidence concerning the overproduction of nitric oxide by inducible nitric oxide synthase and, to a lesser extent, by constitutive nitric oxide synthase(s), especially during the early phases of septic shock^{5,6}. The beneficial effects of inhibition of the production of nitric oxide in human septic shock⁷ and in experimental endotoxaemia⁸ also support the pivotal role of nitric oxide in endotoxin-associated low-perfusion states.

Aminoguanidine, a molecule containing the guanidino group of L-arginine linked to hydrazine, is a relatively selective inhibitor of inducible nitric oxide synthase⁹ which

exerts beneficial effects in experimentally induced Gram-positive¹⁰ and Gram-negative¹¹ shock. It inhibits endotoxin-induced bacterial translocation through the intestinal wall¹² but also has actions that are probably unrelated to inhibition of nitric oxide synthase. Aminoguanidine also inhibits histamine metabolism¹³, polyamine catabolism¹⁴, catalase activity¹⁵ and decreases the formation of glycosylation end-products¹⁶ which may augment its beneficial effects in endotoxin-induced pathology.

Since blood flow to the mesenteric vascular bed is of crucial significance in patients with multiple organ failure¹⁷ and endotoxin decreases the mesenteric blood flow while attenuating the responsiveness to noradrenaline-induced vasoconstriction¹⁸, the aim of this study was to investigate the effects of inducible nitric oxide synthase inhibition on endotoxin-induced mesenteric blood flow and vascular

hyporesponsiveness to vasoconstriction, by using aminoguanidine in anaesthetized rats.

Materials and methods

Animals

Twenty male Sprague-Dawley rats (180–230 g) were obtained from the Laboratory Animal Husbandry Facility of the Department of Pharmacology, Faculty of Medicine, Hacettepe University and were housed under environmentally controlled conditions at $21 \pm 2^\circ\text{C}$ and 30–70 per cent relative humidity with a 12-h dark/12-h light illumination sequence, with free access to tap water (drinking bottle) and standard pellet dairy chow (Murat Yem Sanayii, Ankara, Turkey). All of the procedures in this study were approved by the relevant committees of both departments and the Guiding Principles in the Care and Use of Laboratory Animals were strictly adhered to at all times together with the recommendations from the Declaration of Helsinki.

Drug administration

The 20 rats were allocated randomly into one of four groups according to a four-cell Latin square design that comprised endotoxin and aminoguanidine as two possibly interacting treatment parameters. Endotoxin derived from *Escherichia coli* (lipopolysaccharide 055:B5; 1 mg/kg) or an equivalent volume (1 ml/kg) of non-pyrogenic sterile saline (0.9 per cent w/v, dissolved in pyrogen-free distilled water) was given by intraperitoneal injection to animals in groups 1 and 2, 4 h before they underwent surgery. The dose of endotoxin was chosen on the basis of previous studies in this unit which demonstrated significant *in vivo* effects at a minimum possible dose¹⁹. Similarly, the timing of endotoxin administration was chosen after previous studies reported that inducible nitric oxide synthase activity reached its maximum within 2–6 h after endotoxin administration²⁰. In groups 3 and 4, aminoguanidine 15 mg/kg, a relatively selective inhibitor of the inducible isoform of nitric oxide synthase, or its solvent saline (1 ml/kg) was also given by intraperitoneal injection, 20 min before and 2 h after the endotoxin or saline injections.

In a separate set of experiments on the same animals, vascular responsiveness to vasoconstrictor agents was investigated by injecting phenylephrine 1–30 µg/kg into the jugular vein via a cannula, after which changes in absolute mesenteric blood flow readings were recorded and dose–response curves were constructed.

All drugs were prepared daily, dissolved in non-pyrogenic sterile saline and warmed to body temperature before injection. The drug solutions were kept in a dark container

before injection to protect them from light-induced decomposition.

Surgical procedure

Rats were anaesthetized with intraperitoneal sodium pentobarbitone 60 mg/kg and placed on a heat-insulated cork sheet-covered operating table. The animals were allowed to breathe room air spontaneously. Systolic and diastolic variation in the arterial blood pressure was monitored from a heparinized cannula inserted into the left carotid artery which was connected to a Statham pressure transducer (PX23L, Harvard Apparatus, Boston, Massachusetts, USA) and displayed on a Harvard Oscillograph Pen-recorder (Harvard Apparatus). The left jugular vein was cannulated for drug administration. Body temperature of the rats (37°C) was stabilized within 0.1°C limits by a rectal thermistor probe-controlled incandescent lamp (100 W) placed approximately 30 cm above the abdominal region.

At midline laparotomy, a perivascular Doppler flow probe was placed around the common mesenteric artery trunk and connected to a Transonic Small Animal Flowmeter System T106 (Transonic, Ithaca, New York, USA), which gives absolute blood flow readings (in millilitres per minute). The signals from the flowmeter were also recorded on the Harvard Oscillograph Pen-recorder. Data were expressed as vascular resistance (millimetres of mercury per minute per millilitre) which was calculated by dividing the instantaneous mean arterial blood pressure by the mean arterial blood flow at the corresponding time point. The construction of pressor dose–response curves for phenylephrine was commenced 15 min after stabilization.

Statistical analysis

Data were expressed as mean(s.e.m.) of the number of experiments. Differences between the means of groups were analysed by using paired or unpaired Student's *t* test where appropriate, while two-way analysis of variance (ANOVA) for repeated measurements was performed using a computer program²¹ to analyse the differences between phenylephrine-induced mesenteric blood flow alteration curves²². $P < 0.05$ was accepted as statistically significant.

Results

Blood pressure

Intraperitoneal administration of endotoxin 1 mg/kg 4 h before the surgical procedure resulted in a lower mean

arterial blood pressure at operation (saline-treated group 102.0(7.5) mmHg *versus* endotoxin-treated group 79.0(7.1) mmHg; $n = 5$, P not significant) (Fig. 1). Aminoguanidine had no significant effect on the blood pressure in either treatment group.

Regional blood flow and resistance

In contrast to blood pressure results, endotoxin significantly decreased the mean mesenteric blood flow (saline 13.9(1.5) ml/min *versus* endotoxin 6.1(1.0) ml/min; $n = 5$, $P = 0.0159$). Aminoguanidine blocked the endotoxin-induced decrease without significantly modifying the mesenteric blood flow in solvent (saline)-treated control animals (Fig. 2). The endotoxin-induced fall in mesenteric blood flow could be explained by an increase in the resistance of the mesenteric vascular bed since there was a significant ($P = 0.0099$) difference in mesenteric arterial resistance between saline- and endotoxin-treated animals (Fig. 3). Similarly, aminoguanidine abolished the endotoxin-induced increase in vascular resistance without altering the values calculated in control animals.

Responsiveness to phenylephrine

Intravenous administration of phenylephrine (1–30 μ g/kg) produced a dose-dependent increase in the mean arterial

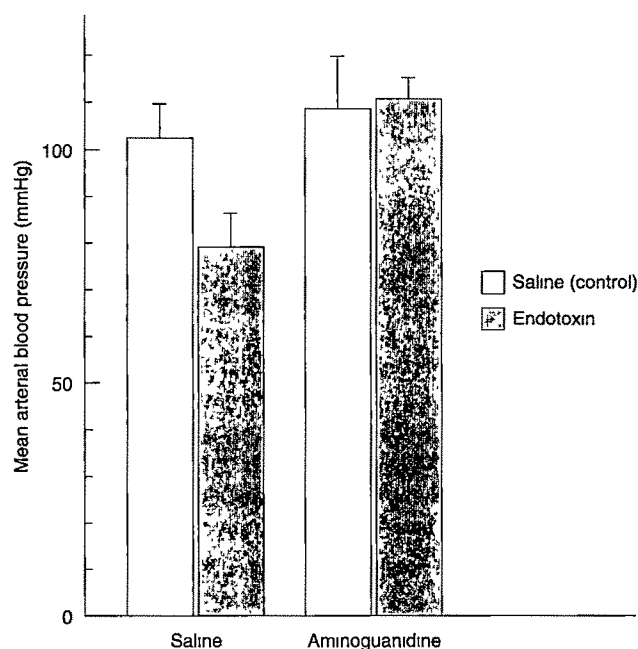


Fig. 1 Mean(s.e.m.) arterial blood pressure 4 h after endotoxin 1 mg/kg or saline (control) injection in rats pretreated with aminoguanidine or saline ($n = 5$ per group)

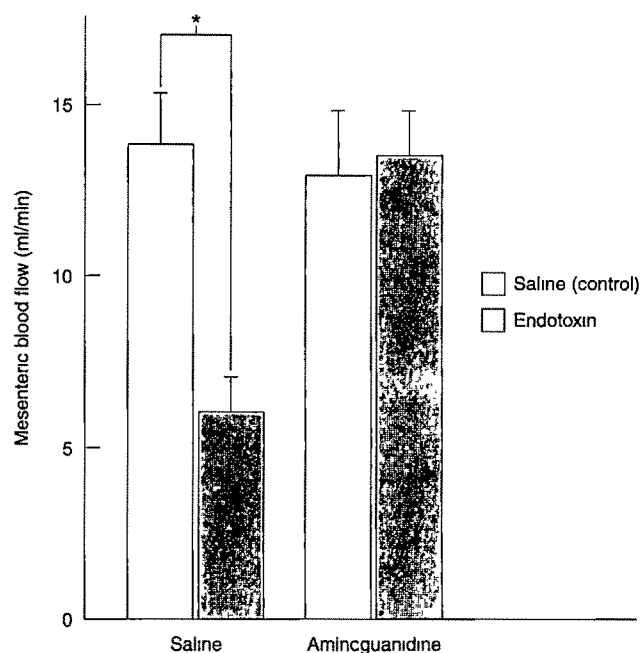


Fig. 2 Mean(s.e.m.) mesenteric arterial blood flow 4 h after endotoxin 1 mg/kg or saline (control) injection in rats pretreated with aminoguanidine or saline ($n = 5$ per group). * $P = 0.0159$ (Student's t test)

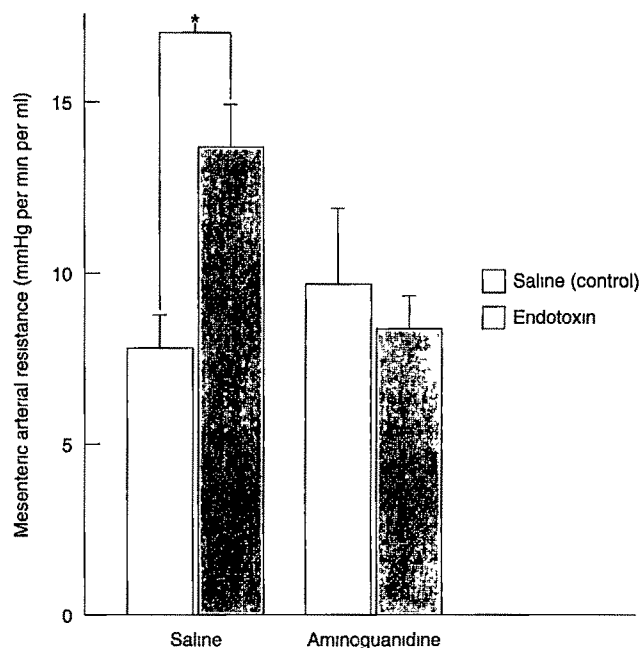


Fig. 3 Mean(s.e.m.) mesenteric arterial resistance 4 h after endotoxin 1 mg/kg or saline (control) injection in rats pretreated with aminoguanidine or saline ($n = 5$ per group). * $P = 0.0099$ (Student's t test)

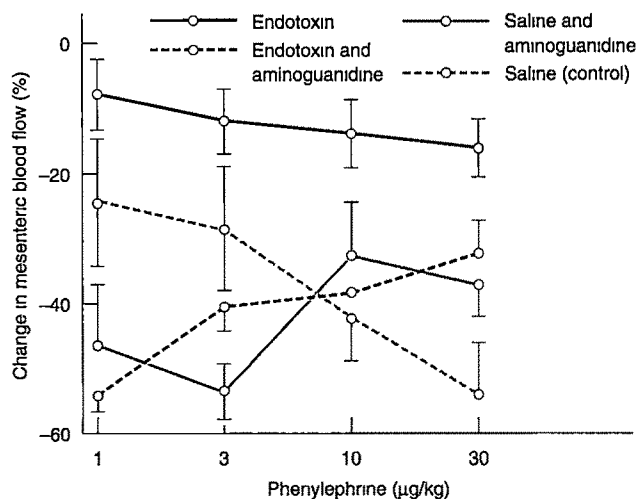


Fig. 4 Dose-response curves for effect of intravenous phenylephrine 1–30 µg/kg on mesenteric blood flow in rats treated with saline (control), endotoxin 1 mg/kg, saline (endotoxin solvent) with aminoguanidine or endotoxin with aminoguanidine. Values are mean (s.e.m.) ($n = 5$); some error bars have been omitted for clarity. Two-way analysis of variance for repeated measures applied to the four curves indicated the significance of the effect of endotoxin ($P < 0.02$), the effect of aminoguanidine ($P < 0.01$) and the interaction ($P < 0.05$)

blood pressure and decreased the mesenteric blood flow by increasing the resistance of the mesenteric vascular bed in all treatment groups (Fig. 4). However, the responsiveness to phenylephrine was significantly attenuated by endotoxin ($P = 0.0117$, two-way ANOVA for repeated measurements applied to phenylephrine dose-response curves for saline-*versus* endotoxin-treated animals). Aminoguanidine restored the responsiveness to phenylephrine without modifying the corresponding control responses. There was no significant difference between any two of the three dose-response curves (saline, saline and aminoguanidine or endotoxin and aminoguanidine) suggesting that aminoguanidine interacted significantly with endotoxin. It is also noteworthy that the trend of the curve obtained from animals treated with both endotoxin and aminoguanidine was different from that of the other three curves (point-to-point analysis applied to the values of 1 µg/kg and 30 µg/kg doses of phenylephrine in endotoxin and aminoguanidine-treated animals revealed a significant difference ($P = 0.0055$), while no such difference was observed with any other of the data point pairs within the other curves).

Discussion

The present study demonstrated that endotoxin decreases mesenteric blood flow by increasing the mesenteric vascular

resistance. It also impairs the response to exogenous phenylephrine. The relatively specific inducible nitric oxide synthase inhibitor aminoguanidine inhibited the effects of endotoxin in anaesthetized rats. At least some of the beneficial effects of aminoguanidine in reversing the effects of endotoxin might not be explained solely by inhibition of inducible nitric oxide synthase.

Administration of endotoxin induces calcium-independent inducible nitric oxide synthase in various tissues including blood vessels²³ and myocardium^{20,24}. It is possible that the blocking effects of aminoguanidine on hyporesponsiveness to phenylephrine in the present study were due to inhibition of nitric oxide production. This hypothesis is supported by the fact that aminoguanidine has been shown to exert beneficial effects in various types of experimental shock^{10,11}. Moreover, the timing of the measurement of changes in mesenteric blood flow in this study (4 h after endotoxin) probably coincided with the maximum nitric oxide production in rats²⁵, which peaks 2–6 h after endotoxin injection²⁶. Although the pharmacokinetic profile of aminoguanidine was not measured in these animals, its slow tissue penetration²⁷ combined with the method of administration (20 min before and 2 h after the endotoxin injection) at a moderate dose of 15 mg/kg should ensure an adequate tissue concentration. Thus, the impaired response to phenylephrine in endotoxin-treated animals might be explained by the increased production of nitric oxide within vascular smooth muscle cells, since there exists abundant evidence for nitric oxide generation during endotoxaemia^{6,8,25,28,29}. Sodium nitroprusside, a nitric oxide donor, has been found to mimic endotoxin-induced vascular hyporesponsiveness *in vivo*³⁰.

Increased production of nitric oxide alone within the mesenteric circulation is unlikely to explain these findings fully, as the vasodilatory effect of nitric oxide would have been expected to increase mesenteric blood flow and decrease mesenteric vascular resistance. The significant increase in the resistance of the mesenteric vascular bed produced by endotoxin in the present study suggests the involvement of vasoconstrictor mechanisms, such as the release of endogenous catecholamines or endothelin 1. Indeed, it was recently discovered that bosentan, a highly specific endothelin antagonist, significantly inhibited endotoxin-induced weight increase and tissue damage in the spleen and liver in mice, while L-canavanine, another specific inducible nitric oxide synthase inhibitor, was ineffective³¹.

Another possible explanation for the increase in mesenteric vascular resistance in response to endotoxin and its reversal by aminoguanidine might relate to protection of the endothelium. Endothelial damage increases mesenteric vascular resistance and aminoguanidine, by interfering with the production of peroxynitrite derived from nitric oxide,

may reduce the effects of free radicals and offer a salvage to the endothelium. This explanation is supported by the results of a recent study which showed that the inhibition of inducible nitric oxide synthase by L-canavanine reduced the endothelial damage produced by endotoxin³². Thus, the beneficial effects of aminoguanidine may be explained by endothelial protection mediated either by inhibition of inducible nitric oxide synthase or by inhibition of the oxidative stress. However, aminoguanidine was relatively ineffective in restoring the responsiveness of isolated rat aortic rings obtained from endotoxaemic animals to noradrenaline *in vitro*¹¹, and this evidence combined with the present observation of the trend of the curve to phenylephrine obtained from animals treated with both aminoguanidine and endotoxin remains to be explained.

Although aminoguanidine is a relatively specific inhibitor of inducible nitric oxide synthase activity and expression⁸, its other pharmacological properties include inhibition of histamine metabolism¹³, polyamine catabolism¹⁴, catalase activity¹⁵, formation of glycosylation end-products¹⁶ or oxidative stress and lipoperoxidation³³ and may help explain the present findings. Recent arguments against a pivotal role of nitric oxide during sepsis⁴ and the results of a study by MacMicking *et al.*³ can also be taken as evidence against inducible nitric oxide synthase inhibition being the only mechanism to explain the beneficial effects of aminoguanidine in the present study. Also, the recently introduced fact of aminoguanidine being a highly specific, but a relatively weak, inhibitor of inducible nitric oxide synthase in comparison to newly developed isothiourea derivatives³⁴ mandates the revision of the concept of inducible nitric oxide inhibition being the only explanation for the beneficial effects of aminoguanidine in endotoxaemia. On the other hand, aminoguanidine is capable of inhibiting both the induction and the activity of the already-induced nitric oxide synthase⁸; it remains a potential therapeutic agent in patients with endotoxaemia.

Acknowledgements

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Arterial intervention and reduction in amputation for chronic critical leg ischaemia

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Background: Untreated chronic critical leg ischaemia (CLI) usually leads to an amputation or death of a patient. Surgical and endovascular interventions may improve arterial flow. Long infrainguinal reconstruction may be the most useful method for preventing amputations. The value of different reconstruction methods was assessed by their impact on amputation incidence.

Methods: A nationwide 2-year analysis of the incidence of major amputations and reconstructions for CLI was done in Finland (population 5.1 million). Incidences were compared in hospital regions with more than 150 000 inhabitants.

Results: The overall amputation incidence was 216 per million inhabitants per year. The corresponding incidence of arterial reconstructions was 203 per million inhabitants per year. There were large variations in the incidence of amputations and reconstructions; 20-fold differences in infrapopliteal surgical reconstructions and 30-fold differences in endovascular procedures were found. There was a correlation between a high incidence of infrapopliteal surgical reconstructions and a low incidence of amputations. This correlation was found for below-knee amputations only.

Conclusion: These results suggest that long surgical reconstructions improving perfusion directly to the ischaemic tissue can improve leg salvage.

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Introduction

The incidence of chronic critical leg ischaemia (CLI) increases with increasing age. As the proportion of the population older than 65 years is growing rapidly, treatment of CLI will increase the workload of vascular surgeons. Cost containment and priorities in the health sector may restrict use of society's resources to serious health problems, excluding or reducing resources for treatment of subjective symptoms like claudication. CLI threatens a patient's life and limb, and causes suffering and a reduced quality of life. Amputation used to be the primary treatment to save the life of a patient.

Reconstructive arterial surgery has reduced the need for amputation. CLI is often the result of widespread arterial occlusions, necessitating long bypasses to crural or even pedal arteries to save a limb^{1,2}. Long bypasses have a high failure rate despite refined surgical technique, use of optimal materials and close follow-up. To avoid the difficulties associated with surgical reconstruction, endovascular procedures such as angioplasty have been used

increasingly, giving a similar outcome with lower costs and fewer complications. Despite excellent results in institutional reports^{3–5}, doubts have been cast about whether vascular surgery and endovascular procedures can reduce the incidence of amputation⁶. Opinions also vary on the optimal method of revascularization for CLI. The present situation for CLI treatment is comparable to that of carotid surgery before the large randomized trials of surgery^{7,8}. The present study was undertaken to clarify the association between different treatments for CLI and the incidence of amputation.

Materials and methods

Finland has a population of 5.1 million. The country has 21 hospital regions served by five university hospitals and 16 regional (central) hospitals. Within the regions there are an additional 22 district hospitals. Vascular surgery is done in the university and regional hospitals and a few bigger district hospitals. Amputations are done in all hospitals.

Amputation data were acquired from the Finnish national health authority (STAKES) which by law gets information on all patient discharges from all hospitals in Finland. These patient data are collected continuously in a national registry and include patient identification information, diagnoses and surgical in-hospital procedures. The patient's domicile is specified in the registry. Information on the population of each hospital region for each year is also available. Based on this information the amputation incidence for each hospital region was calculated.

Only major amputations (above ankle level) for ischaemia (arteriosclerosis and diabetes) were considered relevant to the analysis. The total incidence of amputations and the incidence of below-knee and above-knee amputations were all analysed.

Data on vascular reconstructions were acquired from two sources, the Finnish Vascular Registry FINNVASC and STAKES. Participation in the FINNVASC registry is voluntary and relies on the activity of the vascular surgeon in each participating hospital. All university and regional hospitals in Finland and four big district hospitals participate in the FINNVASC registry. Of all vascular interventions for chronic leg ischaemia in Finland, 98 per cent are done in these hospitals. The other 2 per cent are done in private hospitals that do not participate in the registry. Information on methods of data collection, registration and the validity of registered data has been published previously⁹⁻¹¹. Registration of patient data is anonymized owing to secrecy regulations in Finland. Information on indications, risk factors, procedures, complications and outcome is registered, with a 30-day follow-up. Follow-up data later than 1 month after the procedure are not registered in FINNVASC. As registration of data according to earlier validity control was done with varying accuracy between hospital regions⁹, the registration accuracy of infrapopliteal surgical arterial procedures was checked against data from the STAKES registry. Cross-checking of endovascular procedures done by radiologists was not possible as they are not registered by STAKES. The STAKES registry does not record the indication for intervention, i.e. CLI or claudication, and the numbers were therefore checked against the total number of the corresponding operations in the FINNVASC registry. Infrapopliteal reconstructions were cross-checked as 84 per cent of these were done for CLI according to the FINNVASC registry, while the corresponding figure for reconstructions to the popliteal artery was only 33 per cent. It was not possible to link individual patient data on amputations with specific reconstructions, as only anonymized data were available from both the STAKES and FINNVASC registries. However, regional incidences of reconstructions and amputations could be compared.

Incidences for reconstructions were calculated in the same way as those for amputations.

Information on amputations and arterial reconstructions was acquired for the years 1993 and 1994, and a mean incidence for the 2 years was used. Data on amputations and reconstructions were analysed for each hospital region. However, data from Helsinki and Uusimaa regions were pooled as patients from some parts of Uusimaa are treated in hospitals in Helsinki and it was impossible to separate the vascular reconstruction data according to residence.

For analysis of the impact of vascular reconstructions on the incidence of amputation, the following categories of interventions for CLI were analysed from the FINNVASC data: all interventions, all surgical interventions, infrainguinal surgical reconstructions, infrapopliteal (to crural and pedal arteries) surgical reconstructions, all endovascular procedures, infrainguinal endovascular procedures and infrapopliteal endovascular procedures.

To avoid variations caused by small population samples and variations from one year to another the association between amputation and reconstruction incidence was calculated for only 14 regions with a population over 150 000 inhabitants.

Correlations were calculated with the Spearman rank correlation coefficient and significance as two-tailed.

Results

The number of registered procedures is presented in *Table 1*. The incidence of amputation in the different hospital regions varied greatly: the highest incidence was more than twice the lowest (*Table 2*). Some 63 per cent of the patients who had an amputation were diabetic; the percentage varied between 45 and 79 per cent in the different hospital regions. Large variations were found in the incidence of arterial interventions for CLI. The overall intervention rate varied by more than fivefold, but 20-fold

Table 1 Interventions for chronic leg ischaemia in Finland, 1993–1994

	FINNVASC	STAKES
Reconstructions for chronic leg ischaemia		
Surgical	3258	3394
Endovascular	2992	
Reconstructions for critical ischaemia		
Surgical	1224	
Endovascular	971	
Amputations for critical ischaemia		
Below knee		1185
Above knee		1274

differences were found in the number of infrapopliteal surgical reconstructions and more than 30-fold in infrainguinal endovascular procedures. Diabetes was less common in patients having a reconstruction for CLI than in those having an amputation. As arteriosclerosis has a higher prevalence in the eastern part of Finland, a geographical analysis of amputation incidence was plotted (Fig. 1). No clear geographical pattern explaining the variation in the incidence of amputations could be seen.

Relating the incidence of arterial interventions for CLI to the incidence of amputation did not show any effect of the number of all interventions for CLI (Table 3), or the total number of surgical or endovascular procedures for CLI. There was a correlation between a high incidence of infrapopliteal surgical reconstructions and a low incidence of all amputations ($P=0.027$). However, this correlation was found for below-knee amputations only ($P=0.013$). There was no correlation for the incidence of above-knee amputations ($P=0.325$). The number of endovascular

procedures showed no correlation with amputation incidence.

Cross-checking the registered numbers of infrapopliteal surgical reconstructions in STAKES and FINNVASC registries did not change the outcome of the analysis.

Table 2 Incidence of amputations and arterial reconstructions for critical leg ischaemia in Finnish hospital regions, 1993–1994

	Incidence (per million inhabitants per year)
Amputations	216 (140–330)
Arterial interventions	203 (72–353)
Surgical	112 (52–198)
Infrainguinal	62 (23–143)
Infrapopliteal	33 (6–123)
Endovascular	92 (16–264)
Infrainguinal	72 (7–248)
Infrapopliteal	26 (0–125)

Values are mean (range). Amputation data are from the STAKES registry and reconstruction data from the FINNVASC registry

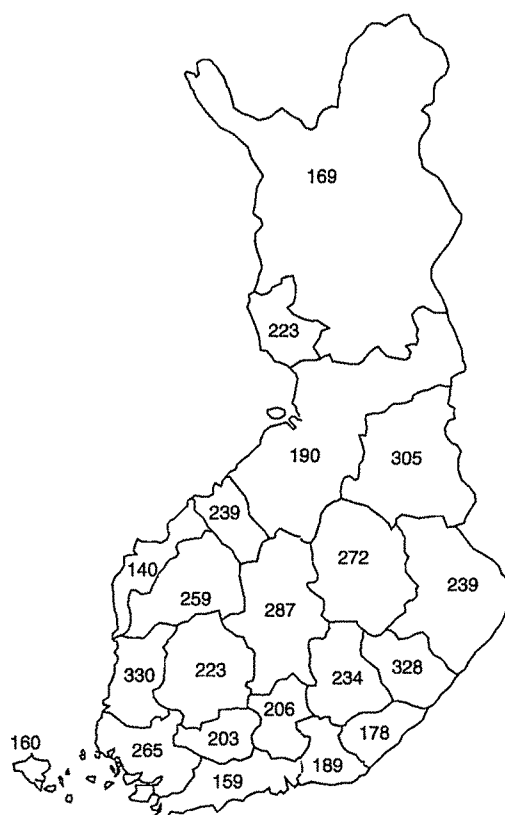


Fig. 1 Incidence of amputations (number per year per million inhabitants) in Finnish hospital regions, 1993–1994 (data from STAKES)

Table 3 Correlation of amputation incidence to number of reconstructions for critical leg ischaemia in hospital districts with more than 150 000 inhabitants in 1993–1994

	All amputations		Above knee		Below knee	
	Spearman's ρ	P	Spearman's ρ	P	Spearman's ρ	P
All reconstructions	-0.132	0.668	-0.187	0.541	-0.077	0.803
Surgical reconstructions						
All	-0.297	0.325	-0.374	0.209	-0.225	0.459
Infrainguinal	-0.418	0.156	-0.297	0.325	-0.396	0.181
Infrapopliteal	-0.610	0.027	-0.236	0.437	-0.665	0.013
Endovascular reconstructions						
All	-0.027	0.929	-0.121	0.694	0.000	1.000
Infrainguinal	-0.088	0.775	-0.121	0.694	-0.033	0.915
Infrapopliteal	-0.293	0.332	-0.160	0.601	-0.276	0.361

Amputation data are from the STAKES registry and reconstruction data from the FINNVASC registry

Discussion

Improving surgical technique and a variety of endovascular treatment methods have greatly increased the number of vascular reconstructions done in different arterial territories. In carotid surgery, large randomized trials have identified patient groups with an indisputable benefit from surgery^{7,8}, and have also identified surgical quality standards necessary to achieve a beneficial outcome. The uncertainty about the value of surgery for CLI is comparable to that for carotid arterial occlusive disease before the trials, even though the prognosis may be even worse for CLI. The grim prognosis of CLI and improved treatment methods have initiated active intervention policies to reduce the incidence of amputation. This has been supported by studies showing that the quality of life for a patient is reduced after an amputation^{12,13}. Increasing numbers of surgical and endovascular interventions are being done^{5,6,14}. Vascular surgery is costly as reintervention is often necessary; the patients are old and often need prolonged hospitalization or institutional treatment¹⁵⁻¹⁸. These problems are further enhanced as the oldest age groups in the population are increasing^{1,19}. Institutional reports have shown excellent clinical patient outcome after arterial reconstruction^{3,5}, but may be misleading in the evaluation of the impact of treatment in the population²⁰. Selection of patients and choice of treatment method apparently influence the outcome. Recent reports on surgery and endovascular treatment have also given less favourable views²¹⁻²³. Previous comparisons of amputation incidence with arterial reconstruction activity in the population have raised serious doubts about the value of arterial reconstruction in preventing amputations^{6,14,24}. The impact of arterial reconstruction on amputation incidence is at present unclear^{1,14,19,23-26}.

National registries with information on amputations and detailed information on reconstructions make it possible to analyse the impact of various methods of arterial revascularization on the incidence of amputation. The present study compared hospital regions in Finland. A similar comparison covering a smaller population has been done in Sweden²⁶. To avoid the influence of chance in small samples, the mean incidences for 2 years in regions with more than 150 000 inhabitants were included in the present study. Correlation between the number of the same procedures in the two registries, FINNVASC and STAKES, was good, reducing the possibility of incomplete registration as the main explanation for the findings. Regrettably, a similar cross-checking of endovascular procedures was not possible.

The incidence of arteriosclerosis in Finland is higher in the eastern than in the western part of the country,

as reflected in the high intervention rates for arterial disease^{10,27}. The incidence of amputations did not follow the expected pattern and was extremely variable.

The large variation in surgical and endovascular treatment of CLI was astonishing as more than tenfold differences were found. These variations can be explained at least in part by varying resources in the hospitals; vascular surgery is mostly done by one to three surgeons, even in regional hospitals, and endovascular procedures by one or two radiologists.

The main finding of the study was the correlation between a high incidence of infrapopliteal surgical arterial reconstructions and a low incidence of amputations. Most patients with CLI have their main arterial occlusions in infrainguinal arteries and a large proportion are diabetic, whose arterial disease primarily affects the infrapopliteal arteries²⁸. In this study diabetics still constituted a major proportion of the patients having an amputation. It was shown previously that increasing the number of infrainguinal (and specifically infrapopliteal) surgical reconstructions for CLI, with increasing proportions of diabetics, resulted in a reduction in amputations^{1,18}. The impact of an increased number of reconstructions was more marked for below-knee than above-knee amputations¹. In the present study there was a correlation between the incidence of infrapopliteal reconstructions and fewer below-knee amputations, but not for above-knee amputations. As detailed information on the patients who had an amputation was not available, it was impossible to determine why there was no impact on above-knee amputations. It may be that patients undergoing above-knee amputation tend to be institutionalized and immobile, and reconstruction was not even considered as an alternative^{1,29}. Below-knee amputations are usually done in patients who have a good chance of walking with a prosthesis after the amputation.

The lack of a correlation between endovascular treatment at any level and the incidence of amputation is disappointing. Endovascular treatment has been shown to mainly achieve good results in short stenoses and occlusions in large vessels^{22,30}. Most patients with CLI have widespread and distal disease; endovascular treatment may have only limited value in this setting.

This study showed on a nationwide scale that there was an association between interventional treatment for CLI and the incidence of amputation, but only for surgical reconstructions to infrapopliteal arteries. CLI is one of the main indications for intervention as the population grows older⁶. To ascertain the appropriate treatment methods for CLI, large properly designed studies need to be performed urgently.

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Near-infrared spectroscopy grades the severity of intermittent claudication in diabetics more accurately than ankle pressure measurement

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Background: The aim of this study was to evaluate near-infrared spectroscopy (NIRS), combined with a treadmill-walking test, as a method of assessment of intermittent claudication (IC) in diabetic patients.

Methods: Some 208 symptomatic legs in 153 consecutive patients who complained of calf IC due to atherosclerotic disease were studied with NIRS and resting ankle: brachial pressure index (ABPI).

Results: There was good reproducibility of NIRS measurements. Three distinct types of IC were detected by NIRS. ABPI was significantly different between these three types in non-diabetic patients, but could not grade the severity of IC in diabetic patients. Recovery time (RT) of muscle oxygenation differentiated more accurately between severe and moderate claudication than ABPI in diabetics, although RT and ABPI had similar accuracy in non-diabetics. There was a significant correlation between RT and ABPI in non-diabetic patients and patients who had been diabetic for less than 10 years, while there was no correlation in patients who had had diabetes for over 10 years.

Conclusion: Measurement of muscle oxygenation during exercise by NIRS graded the severity of IC in diabetic patients more accurately than resting ABPI.

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Introduction

Although diabetes is one of the major risk factors for intermittent claudication (IC)^{1,2}, it is difficult to assess accurately the severity of IC in diabetic patients using the ankle:brachial pressure index (ABPI). Calcification of arteries in diabetics can interfere with ABPI measurement. Walking distance is affected by a patient's subjective perception, so it cannot be considered an accurate measure of IC³.

Near-infrared spectroscopy (NIRS) is a recent technique for assessing muscle oxygenation non-invasively in patients with peripheral vascular disease (PVD)⁴. The authors⁵ and others^{6,7} have recently reported the use of NIRS, combined with a treadmill-walking test (NIRS-treadmill test), for the objective assessment of IC. It was concluded that NIRS has a potential role in the evaluation of IC, but the reproducibility of the NIRS-treadmill test has not yet been confirmed in patients with PVD.

The aim of this study was to evaluate a NIRS-treadmill test as a method for the assessment of IC in diabetic patients

by comparison with resting ABPI. In addition, the repeatability of the NIRS-treadmill test was examined.

Patients and methods

The protocol used in this study was approved by the local ethics committee. All measurements were made after obtaining the patients' informed consent. Two hundred and eight symptomatic legs in 153 consecutive patients who complained of calf IC due to peripheral atherosclerosis were studied between January 1993 and December 1997. There were 142 men and 11 women with a mean age of 66 (range 43–91) years. Subjects were excluded for the following reasons: venous insufficiency such as varicose veins and deep vein thrombosis, surgical procedures in the preceding 6 months, inability to complete the treadmill walking for reasons other than IC (such as breathlessness and palpitations), or severe cardiopulmonary disease. When NIRS measurements were performed bilaterally and the subject stopped walking because of unilateral calf pain, only the

symptomatic leg was studied; the contralateral leg was excluded.

Assessment of diabetes

Patients were divided into two groups according to the presence of diabetes mellitus. The diagnosis of diabetes was based on a history of treatment with insulin or an oral hypoglycaemic agent, an abnormal glucose tolerance test result, a random blood glucose concentration of 200 mg/dl or more, or a glycosylated haemoglobin A_{1c} level of 6.5 per cent or more. These patients were subdivided into two equally sized groups, according to the duration of the diabetes, into long-term (10 years or more) and recent (less than 10 years) diabetics.

Near-infrared spectroscopy

The optodes of a near-infrared photometer (OM-100A; Shimadzu, Kyoto, Japan) were positioned on the posterior aspect on the calf, over the medial head of the gastrocnemius muscle. The light guide and the near-infrared detector were applied to the skin 4 cm apart longitudinally, and held in place with a bandage. This instrument has been tested previously in muscle studies⁸. Near-infrared light penetrates skin, subcutaneous fat and underlying muscle, and is either absorbed or scattered within the tissues. Part of the scattered light is detected by the detector. The penetration depth is estimated to be about 2 cm^{8,9}. The influence of subcutaneous adipose tissue on near-infrared light propagation in leg muscle and on the sensitivity of the OM-100A has been investigated recently⁸. It was concluded that near-infrared light penetrates shallow regions of muscle under the skin and subcutaneous fat even when the adipose tissue thickness is 1.5 cm¹⁰.

NIRS measurements of the relative changes in oxygenated haemoglobin (HbO₂) and deoxygenated haemoglobin (Hb) were performed with the patient in the standing position: (1) at rest for 3–5 min until a stable baseline was reached; (2) during walking; and (3) during the subsequent recovery period at rest (maximum 10 min). It has previously been reported⁵ that there are three distinct patterns of serial changes in HbO₂ and Hb during walking and resting periods. Patients with a type 0 pattern were characterized by no change in HbO₂ and Hb, and had no complaints of IC during the test. All symptomatic claudicants were included into two groups: type 1 and 2. In these types, HbO₂ decreased and Hb increased a few seconds after the beginning of the exercise, and each reached the respective plateau. At the end of the walk, HbO₂ recovered within 10 min in patients with a type 1 but not type 2 pattern (*Fig. 1*). The interval from the end of the walk to the point at which the two curves crossed

(recovery time; RT) was used as an arbitrary parameter that correlated with the severity of IC⁵.

Near-infrared spectroscopy–treadmill test

After measuring ABPI at rest, the patient stood on the treadmill-walking machine (Aeromiu; Nihon-Koden, Tokyo, Japan). A standard treadmill-walking test¹¹ was performed, with some modification. This treadmill test began at a 0 per cent slope with a speed of 0.8 km/h. The slope was increased gradually to 12 per cent over 30 s, and the speed was increased by 0.8 km/h every 15 s to 2.4 km/h. Walking lasted for as long as each patient was able, with a maximum duration of 5 min. At the end of the walking test, the treadmill slope was returned to 0 per cent. The maximum tolerated walking time was measured in patients who were not able to complete the 5-min walking test.

Reproducibility of near-infrared spectroscopy

Eleven consecutive patients with 21 symptomatic legs (ten men and one woman with a mean age of 67 (range 57–76) years) who were admitted to hospital for a vascular operation underwent repeated NIRS measurements to determine the reproducibility of RT. A NIRS–treadmill test was performed on the same patient at the same time on three different days. The interval between the first and the third tests ranged from 3 to 9 (mean 6) days.

Correlation between recovery time and ankle-brachial pressure index at rest and after exercise

Another cohort of seven patients with 13 symptomatic legs (six men and one woman with a mean age of 68 (range 58–80) years) who were admitted to hospital for a vascular operation underwent the same treadmill test twice, in the morning and afternoon on the same day. In the first test, the NIRS–treadmill examination was performed. In the afternoon, an identical treadmill-walking test was done but the ABPI was measured at 1, 5 and 10 min after exercise.

Statistical analysis

Statistical analyses were performed with Fisher's exact test and χ^2 test for categorical data, and Mann–Whitney *U* test and Fisher's protected least significant difference for continuous data. A bivariate χ^2 test was performed in the comparison of two receiver–operator characteristic (ROC) plots¹². Results were expressed as mean(s.d.). $P < 0.05$ was considered significant. The repeatability for RT and ABPI was analysed by the intraclass correlation coefficient (r_1)¹³. According to this value, agreement was considered almost

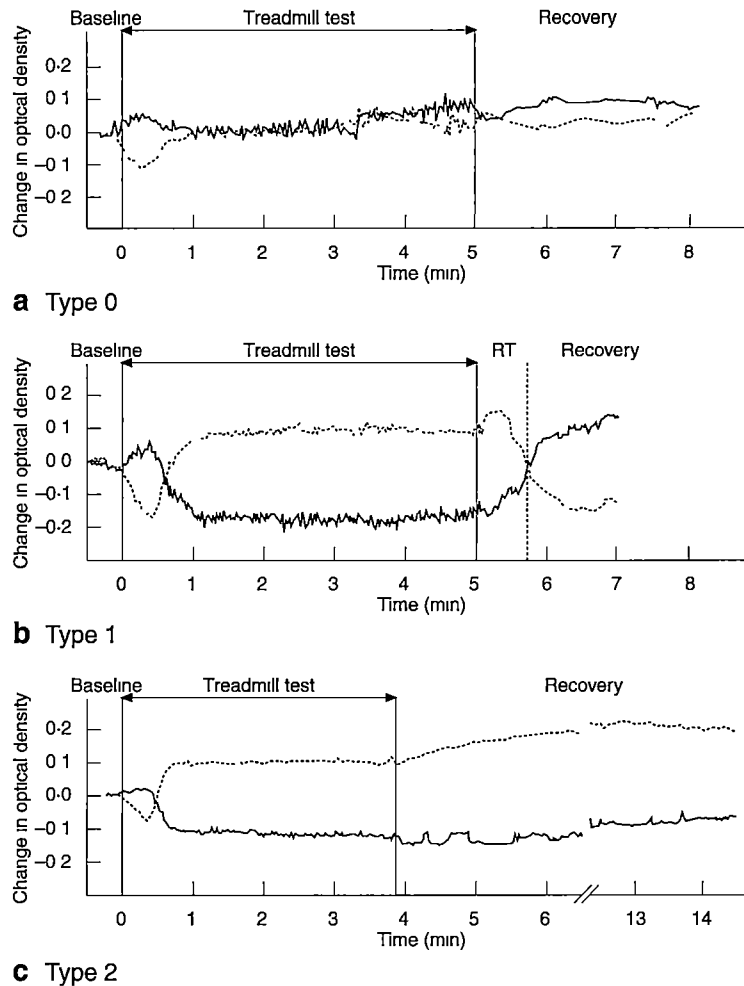


Fig. 1 a Typical type 0, b type 1 and c type 2 tracings of oxygenated haemoglobin (solid line) and deoxygenated haemoglobin (dotted line) during a near-infrared spectroscopy-treadmill-walking test. The solid vertical lines indicate the beginning and the end of walking; the dotted vertical line indicates the crossing point of the two curves. RT, recovery time

perfect ($r_1 \geq 0.81$), substantial ($0.80 \geq r_1 \geq 0.61$), good ($0.60 \geq r_1 \geq 0.41$), fair ($0.40 \geq r_1 \geq 0.21$) or slight ($0.20 \geq r_1$)¹⁴.

Results

Differentiation of severity of diabetes

Sixty-two of 153 patients were diabetic (56 men and six women). There were 31 long-term diabetics (26 men and five women) and 31 recent diabetics (30 men and one woman). The diabetic patients were significantly younger than the non-diabetics (mean age 64(8) versus 67(8) years respectively; $P = 0.022$, Mann-Whitney U test). There were significant differences between recent and long-term diabetics, in treatment ($P = 0.004$, χ^2 test) and complications ($P = 0.011$, Fisher's exact test) (Table 1).

Near-infrared spectroscopy measurements

NIRS measurements were performed in one leg in 58 patients and in two legs in 95 patients who complained of bilateral claudication. In 40 of the 95 patients who had bilateral measurements, the contralateral leg was excluded according to the protocol when claudication developed in only one leg during the exercise. In the remaining 55 measurements, 40 patients completed a 5-min treadmill test, while 15 patients could not finish the test. In the 40 patients with bilateral symmetrical claudication who completed the treadmill test, the combination of NIRS types for the two legs was type 0-type 0 (five patients), type 0-type 1 (12) and type 1-type 1 (23). In 15 patients who were unable to complete the test because of equally severe pain in both legs, the combination of NIRS types in the two legs was type 1-type 1 (12 patients), type 1-type 2 (two) and type

Table 1 Characteristics of diabetic patients

	Recent (<10 years)	Long-term (≥ 10 years)	<i>P</i>
No. of patients	31	31	
Age (years)*	63(8)	64(7)	0.43‡
Treatment			0.004§
Diet	12	2	
Oral agents	16	19	
Insulin	3	10	
Complications†			0.011¶
No	27	17	
Yes	4	14	

*Values are mean(s.d.) †E.g. neuropathy, nephropathy or retinopathy.

‡Mann-Whitney *U* test, § χ^2 test; ¶Fisher's exact test

2-type 2 (one). Measurements for both legs were included in the analysis in patients with equal claudication, because they could not differentiate the leg that was worse.

Results of all NIRS measurements were differentiated into two groups according to the severity of IC (Table 2). There were 64 patients (104 legs) with moderate IC who were able to complete the 5-min treadmill test and 89 patients (104 legs) with severe IC who were unable to complete the test because of severe claudication. There was no significant difference between the patients with moderate and severe IC with respect to mean age ($P=0.99$, Mann-Whitney *U* test). All 208 legs were classified into the three types according to NIRS measurements. All type 0 legs completed the 5-min treadmill walking test and none of the type 2 legs was able to walk for 5 min. There was a significant difference between moderate and severe IC in NIRS types (Table 2).

Results in diabetic patients

Mean values of resting ABPI for each type of NIRS measurement are shown in Fig. 2 for non-diabetic and diabetic legs. There were significant differences between the three types in non-diabetic patients (type 1 and 2 versus type 0, $P<0.0001$; type 2 versus type 1, $P=0.026$; Fisher's protected least significant difference test). In diabetic legs, however, a significant difference was shown only between type 0 and type 1 ($P=0.002$).

The results for all NIRS type 1 legs were examined according to the presence of diabetes. The mean RT in type 1 legs with severe claudication was significantly longer than that in type 1 legs with moderate claudication, both in non-diabetics (1.08(0.57) versus 3.20(2.01) min, $P<0.0001$) and in diabetics (1.26(0.77) versus 3.25(1.92) min, $P<0.0001$) (Mann-Whitney *U* test). The mean ABPI in type 1 legs with severe claudication was also significantly lower than that in type 1 legs with moderate claudication, both in non-

Table 2 Results of near-infrared spectroscopy measurements

	Intermittent claudication		<i>P</i>
	Moderate	Severe	
No. of patients	64	89	
Age (years)*	66(9)	66(7)	0.99†
No. of legs	104	104	
NIRS type			<0.0001 ‡
0	30	0	
1	74	93	
2	0	11	

*Values are mean(s.d.). Moderate claudication, able to complete 5-min treadmill test, severe, unable to complete the test. NIRS, near-infrared spectroscopy. †Mann-Whitney *U* test, ‡ χ^2 test

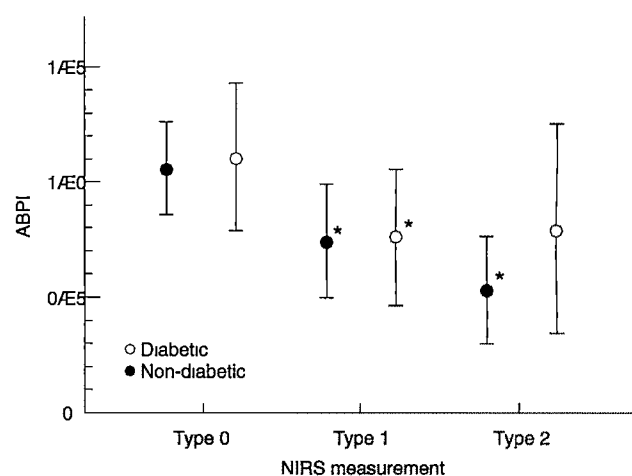


Fig. 2 Mean(s.d.) ankle : brachial pressure index (ABPI) for each type of near-infrared spectroscopy (NIRS) measurement in diabetic and non-diabetic patients. * $P<0.01$ versus type 0; † $P<0.05$ versus type 1 (Fisher's protected least significant difference)

diabetics (0.93(0.20) versus 0.60(0.17), $P<0.0001$) and in diabetics (0.92(0.34) versus 0.64(0.18), $P=0.0001$) (Mann-Whitney *U* test). There were no differences between the number of diabetics in the groups with moderate and severe claudication and NIRS type 1 legs ($P=0.94$, χ^2 test).

Differentiation between severe and moderate claudication with recovery time and ankle : brachial pressure index

To evaluate the sensitivity and specificity of the tests performed in 167 legs with type 1 NIRS results, ROC plots¹² were constructed (Fig. 3). RT was more accurate than ABPI at distinguishing between moderate and severe claudication in diabetics ($P=0.03$) but not in non-diabetic

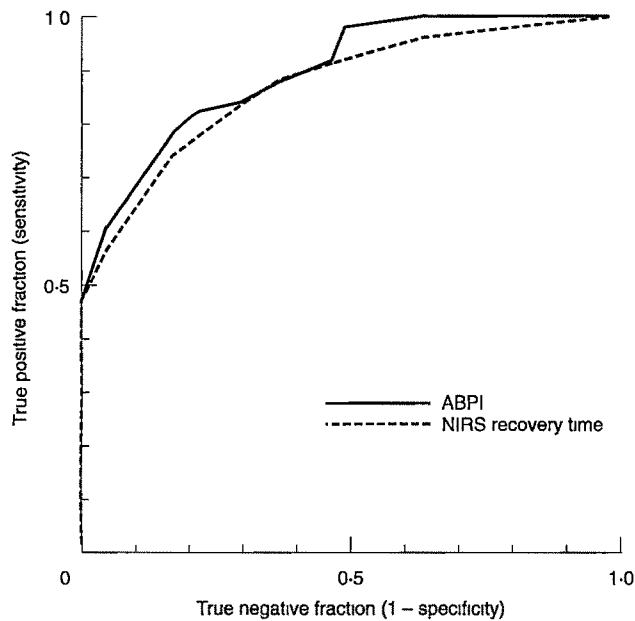
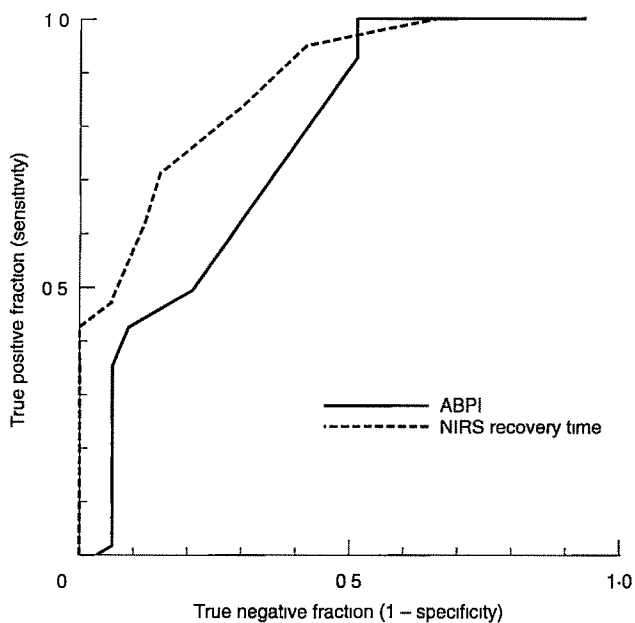
**a Non-diabetic****b Diabetic**

Fig. 3 Receiver-operator characteristic plots for assessing ability of near-infrared spectroscopy (NIRS) recovery time and ankle: brachial pressure index (ABPI) to differentiate severe versus moderate type 1 in **a** non-diabetic and **b** diabetic patients. $P < 0.05$ (ABPI versus recovery time in diabetics); $P < 0.05$ (ABPI in diabetics versus non-diabetics) (bivariate χ^2 test)

legs ($P = 0.48$) (bivariate χ^2 test). A similar accuracy in diabetic and non-diabetic legs was achieved by RT ($P = 0.45$) but not ABPI ($P = 0.025$).

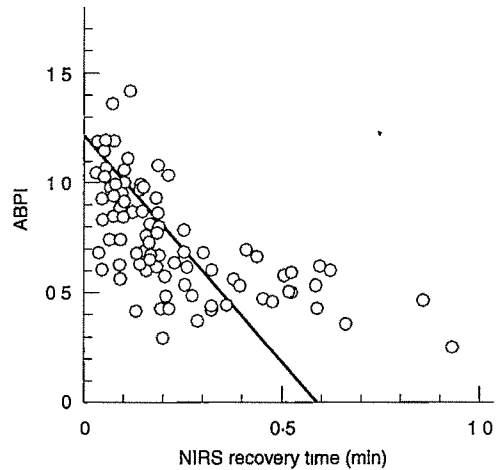
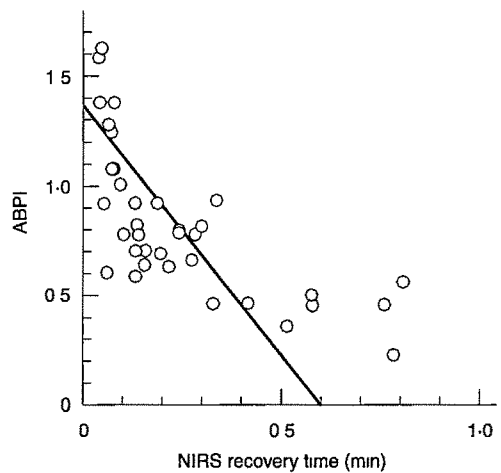
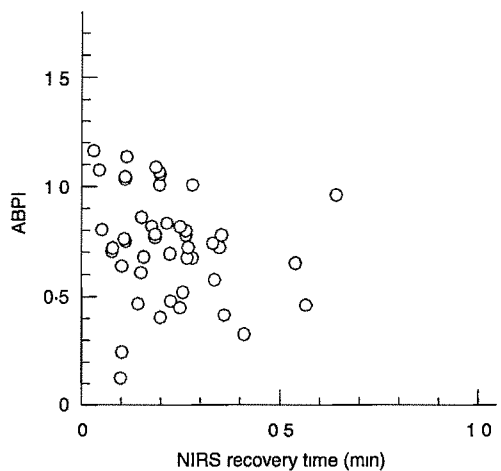
**a Non-diabetic****b Recent diabetic****c Long-term diabetic**

Fig. 4 Correlation between near-infrared spectroscopy (NIRS) recovery time and ankle: brachial pressure index (ABPI) in **a** non-diabetics ($r^2 = 0.40$, $P < 0.0001$), **b** recent diabetics (less than 10 years) ($r^2 = 0.44$, $P < 0.0001$) and **c** long-term diabetics (10 years or more) ($r^2 = 0.03$, $P = 0.28$)

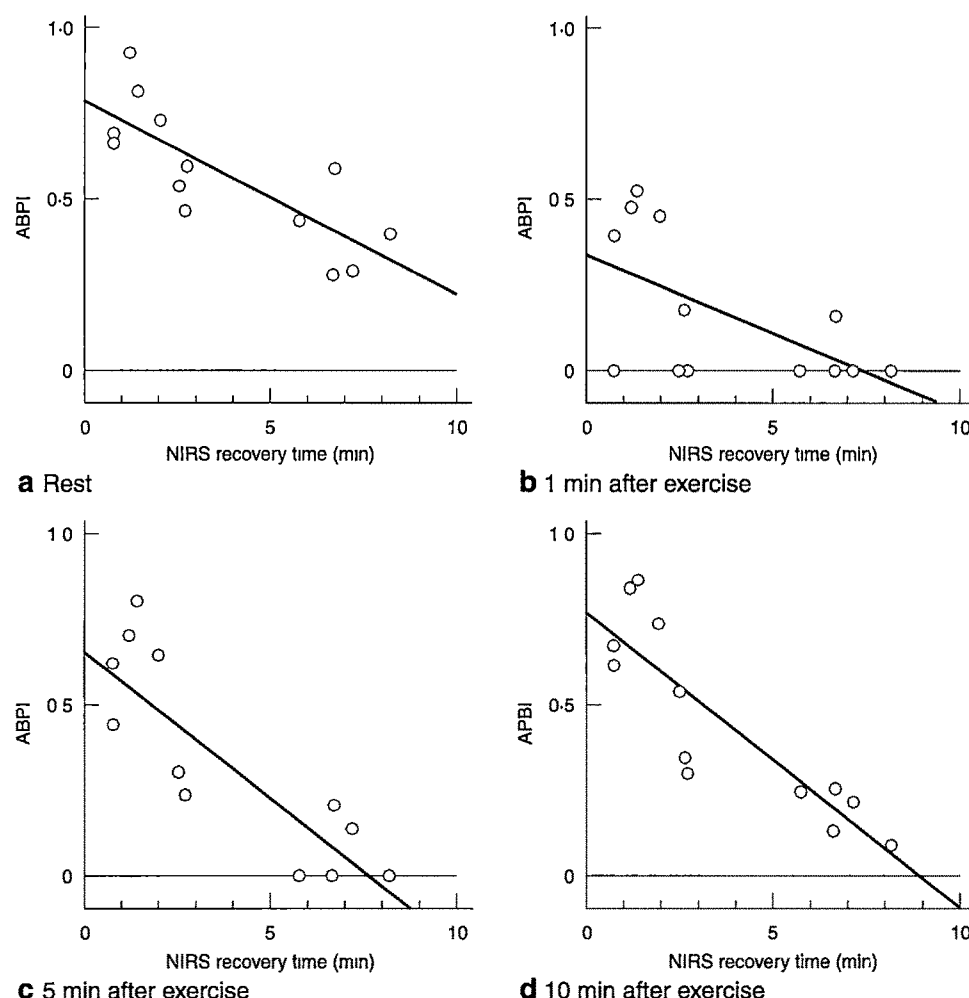


Fig. 5 Correlation between near-infrared spectroscopy (NIRS) recovery time and ankle-brachial pressure index (ABPI) for:

- a ABPI at rest ($r^2 = 0.63$, $P = 0.007$)
- b ABPI at 1 min after exercise ($r^2 = 0.34$, $P = 0.035$)
- c ABPI at 5 min after exercise ($r^2 = 0.69$, $P = 0.002$)
- d ABPI at 10 min after exercise ($r^2 = 0.76$, $P < 0.001$)

Correlation between recovery time and ankle-brachial pressure index in diabetic patients

There was a significant correlation between RT and ABPI in non-diabetic patients ($r^2 = 0.40$, $P < 0.0001$) and in patients who had been diabetic for less than 10 years ($r^2 = 0.44$, $P < 0.0001$) (Fig. 4). There was no significant correlation in patients who had had diabetes for more than 10 years ($r^2 = 0.03$, $P = 0.28$).

Repeatability of near-infrared spectroscopy measurements

Sixty-three measurements of NIRS in 21 symptomatic legs in 11 patients (ten men and one woman) were performed.

Two legs were type 0 and 19 were type 1. There were no type 2 legs. In the 19 type 1 legs, the mean(s.d.) value of RT at the first measurement was 3.63(2.61) (range 1.26–9.49) min and the mean(s.d.) value of ABPI was 0.63(0.28) (range 0.63–1.18). Almost perfect agreement was found for repeated RT ($r_1 = 0.92$) and ABPI ($r_1 = 0.85$) measurements.

Correlation between recovery time and ankle-brachial pressure index

There was a correlation between RT and ABPI at rest and 1, 5 and 10 min after exercise (Fig. 5). All RT values were significantly correlated to the corresponding ABPI values. The highest correlation was seen in ABPI after 10 min of exercise ($r^2 = 0.76$, $P < 0.001$) (Fig. 5d).

Discussion

IC is an important risk factor in patients with diabetes¹, and is a predictor of systemic PVD¹⁵. According to the natural history of IC, 16 per cent of patients have progressive symptoms, 25 per cent require surgery or experience tissue loss and 4 per cent need a major amputation, over a follow-up of 5 years¹⁶. Although the preventive effects of medication on the progression of PVD are still controversial^{1,17}, the duration of diabetes could have an important role in the development of PVD². In the present study, it was possible to differentiate between patients with severe and moderate diabetes only by taking into account its duration.

Considering the intimate association between diabetes and IC, intensive follow-up is essential in patients with diabetes. Although ABPI remains a useful tool for evaluating IC in outpatients because of its ease and low cost, it is well known that the resting ABPI fails to reflect the severity of IC in diabetic patients¹⁸.

In this study, the limitations of ABPI in diabetic patients were explored compared with NIRS. Because the recovery of muscle oxygenation after exercise is mainly dependent on blood flow, RT and ABPI showed a significant correlation as expected (Figs 4 and 5). However, the results suggest that resting ABPI has a significant limitation compared with RT for assessment of claudication in diabetic patients, because of a poor correlation between ABPI and RT in long-term diabetics (Fig. 4c) and the diagnostic inaccuracy of resting ABPI compared with RT (Fig. 3b).

Toe pressure measurement may be preferable for assessing severe foot ischaemia in diabetics^{11,18}, but its value for assessing calf claudication is not clear. Akbari and LoGerfo¹⁹ have recently reviewed the limitations of various other non-invasive tests in patients with diabetes. The basis of calf claudication lies in functional ischaemia of the calf muscles during exercise²⁰, so it is necessary to use stress testing to assess IC.

The various stress tests have common problems. Walking distance is easily affected by a patient's subjective perception and attitude²¹, so that it cannot be considered an accurate parameter of claudication. Moreover, Watson *et al.*³ have indicated recently that claudication distance is poorly estimated and inappropriately measured. The advantage of NIRS is that it can assess the regional oxygenation in the calf muscle directly and non-invasively. Although nuclear magnetic resonance spectroscopy can assess muscle ischaemia in PVD²², it has limited application because of its high cost. Isotope measurement has shown good reproducibility²³, but cannot be used for serial studies. In this study NIRS was shown to be reproducible in patients with IC.

The advantages and problems of NIRS application in muscles have been reviewed recently²⁴; the main problem at

present is the quantification of HbO₂ and Hb. In this study muscle oxygenation was evaluated using the RT after exercise. These results, in which the severity of PVD was reflected by the resaturation of muscle after exercise, confirm previous reports⁵⁻⁷. NIRS measurements of muscle blood flow^{7,25} and oxygen consumption with arterial or venous occlusion methods^{4,7} provide other parameters for assessing muscle ischaemia. More recently, continuous measurement of muscle tissue saturation has been provided by various NIRS instruments based on lightguide remittance^{26,27}, spatial resolved²⁸ and phase modulated²⁹ spectroscopy, but the clinical value of these instruments has not been confirmed. NIRS can also be used to monitor the effect of medical treatment on claudication³⁰, to identify PVD in the elderly³¹, to assess the effect of haemodialysis in patients with PVD²⁹ and for perioperative monitoring during vascular surgery²⁸.

In conclusion, measurement of muscle oxygenation during exercise by NIRS differentiated the severity of claudication in diabetic patients more accurately than resting ABPI. NIRS could be used to provide objective information regarding the development of IC in patients with diabetes.

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Morbidity and mortality of inadvertent enterotomy during adhesiotomy

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Background: Inadvertent enterotomy is a feared complication of adhesiotomy during abdominal reoperation. The nature and extent of this adhesion-associated problem are unknown.

Methods: The records of all patients who underwent reoperation between July 1995 and September 1997 were reviewed retrospectively for inadvertent enterotomy, risk factors were analysed using univariate and multivariate parameters, and postoperative morbidity and mortality rates were assessed.

Results: Inadvertent enterotomy occurred in 52 (19 per cent) of 270 reoperations. Dividing adhesions in the lower abdomen and pelvis, in particular, caused bowel injury. In univariate analysis body mass index was significantly higher in patients with inadvertent enterotomy (mean(s.d.) 25.5(4.6) kg/m²) than in those without enterotomy (21.9(4.3) kg/m²) ($P < 0.03$). Patient age and three or more previous laparotomies appeared to be independent parameters predicting inadvertent enterotomy (odds ratio (95 per cent confidence interval) 1.9 (1.3–2.7) and 10.4 (5.0–21.6) respectively; $P < 0.001$). Patients with inadvertent enterotomy had significantly more postoperative complications ($P < 0.01$) and urgent relaparotomies ($P < 0.001$), a higher rate of admission to the intensive care unit ($P < 0.001$) and parenteral nutrition usage ($P < 0.001$), and a longer postoperative hospital stay ($P < 0.001$).

Conclusion: The incidence of inadvertent enterotomy during reoperation is high. This adhesion-related complication has an impact on postoperative morbidity

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Introduction

Postoperative intra-abdominal adhesions are a major concern in modern surgery. Intestinal obstruction is an important and well known clinical consequence of adhesions, resulting in significant morbidity and mortality rates, and high financial costs^{1–4}. Secondary infertility in women and chronic abdominal and pelvic pain are other, frequently cited, adhesion-related problems^{5–7}. Furthermore, intra-abdominal adhesions render reoperation difficult and may increase the complication rate of the intended surgical procedure. Prolonged operating time, unfeasibility of the laparoscopic approach and inadvertent enterotomy are known drawbacks of reoperative abdominal surgery, directly related to adhesions. Recently, Moran⁸ reported that 60 per cent of patients with a history of previous intra-abdominal surgery who underwent elective colorectal surgery had significant adhesions, resulting in prolonged incision time and substantial 'division of adhesions' time. Extensive adhesions are a major reason for conversion from

laparoscopy to laparotomy because of the risk of complications and significantly prolonged operating time^{9,10}.

Inadvertent enterotomy discovered either during surgery or in the first few postoperative days is a dreaded complication of abdominal reoperation. Although all surgeons are familiar with this complication, experience is anecdotal and little evidence has been collected to outline the nature and the extent of this adhesion-related disorder. Detailed knowledge thereof may provide a baseline for evaluating measures to prevent adhesions and newly developed products. In the present study the incidence and the risk factors of inadvertent enterotomy during division of intra-abdominal adhesions were assessed in a cohort of reoperated patients and the clinical consequences were analysed.

Patients and methods

All consecutive patients who underwent abdominal reoperation at which adhesions were divided, between July

1995 and September 1997, were included in the study and their medical records were reviewed retrospectively.

Abdominal reoperation was defined as a laparotomy via a pre-existing incisional scar or part thereof. Patients who underwent relaparotomy for complications of previous abdominal surgery in the same admission period (e.g. postoperative haemorrhage) and those who underwent planned re-exploration for severe intra-abdominal infection were excluded. The last reoperation of patients who underwent more than one reoperation in the study period was analysed and the other procedures were defined as previous operations.

Preoperative and peroperative data including age, sex, body mass index (BMI), number and date of previous laparotomies, indication for operation, level of surgical experience (colorectal surgeon, surgeon, final-year trainee), emergency status of the operation, American Society of

Anesthesiologists (ASA) classification¹¹, and occurrence, localization and treatment of enterotomy were assessed.

Postoperative complications including anastomotic leakage, wound infection, urinary tract infection, intra-abdominal sepsis, fistula formation, bowel obstruction, pneumonia and organ failure were noted, as well as unscheduled admission to the intensive care unit (ICU), the need for urgent relaparotomy and parenteral nutrition, and the length of hospital stay.

Inadvertent enterotomy was defined as that which occurred during the phase of the operation in which adhesions were divided.

Statistical analysis

Differences between patients who had an enterotomy and those who had not were tested using Student's *t* test in the

Table 1 Patient characteristics according to the occurrence of an inadvertent enterotomy

	Inadvertent enterotomy		<i>P</i>
	Yes	No	
Age (years)			<0.05
15–29	1 (5)	18 (95)	
30–44	8 (14)	48 (86)	
45–59	12 (16)	65 (84)	
60–74	21 (24)	67 (76)	
≥75	10 (33)	20 (67)	
Sex			0.51
M	21 (18)	99 (82)	
F	31 (21)	119 (79)	
Body mass index (kg/m ²)*	25.5(4.6)	21.9(4.3)	<0.03
Level of surgical experience			0.49
Colorectal surgeon	20 (21)	75 (79)	
Surgeon	14 (23)	48 (77)	
Final-year trainee	18 (16)	95 (84)	
Emergency status			0.23
Elective	42 (18)	190 (82)	
Emergency	10 (26)	28 (74)	
Previous laparotomies			<0.001
1	14 (10)	122 (90)	
2	9 (12)	66 (88)	
3	12 (40)	18 (60)	
4	7 (50)	7 (50)	
5	4 (50)	4 (50)	
≥6	6 (86)	1 (14)	
Time from last laparotomy to reoperation (years)†	1.7 (0.3–6.3)	2.1 (0.5–6.2)	0.99
Indication for surgery			0.19
Inflammatory bowel disease	10 (16)	53 (84)	
Colonic cancer	7 (14)	43 (86)	
Other abdominal malignancy	4 (11)	31 (89)	
Bowel obstruction	9 (30)	21 (70)	
Diverticular disease	6 (33)	12 (67)	
Aortic aneurysm	4 (33)	8 (67)	
Miscellaneous	12 (19)	50 (81)	

*Values are mean(s.d.) or †median (range), unless otherwise indicated values in parentheses are percentages

case of continuous variables or the Mann–Whitney *U* test in the case of a skewed distribution. Differences across strata of categorical variables (Pearson or likelihood ratio) were tested with the χ^2 test. A stepwise logistic regression analysis was done to identify independent parameters predicting enterotomy. Postoperative results were analysed using the Student *t* test or Mann–Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Two-tailed $P < 0.05$ was considered significant.

Results

Over a period of 26 months, 270 patients underwent abdominal reoperation, 120 men (44 per cent) and 150 women (56 per cent) with a mean age of 55 (range 16–89) years (Table 1).

One or more inadvertent enterotomies occurred in 52 (19 per cent) of 270 reoperations. All except one were small bowel enterotomies. At 31 laparotomies (60 per cent), one enterotomy was made and at the other 21 (40 per cent) more than one enterotomy occurred. Over 50 per cent of enterotomies occurred when adhesions in the lower abdomen and pelvis were divided and 30 per cent when adhesions were divided to enter the abdominal cavity. A total of 33 small bowel resections and 60 suture repairs were carried out to manage the inadvertent enterotomies, excluding enterotomies in bowel segments planned for resection.

Patients with inadvertent enterotomy had undergone a mean of 3.3 (range 1–17) previous laparotomies, which was significantly more than patients without enterotomy who had undergone 1.7 (range 1–6) previous laparotomies ($P < 0.001$). Patients with three or more previous laparotomies appeared to be particularly at risk of an inadvertent enterotomy (Fig. 1).

The mean age of patients with an enterotomy (60.3 years) was significantly higher than that of patients without an enterotomy (54.1 years) ($P < 0.05$). Patients with inadvertent enterotomy had a significantly higher BMI (mean (s.d.) 25.5 (4.6) kg/m²) than those without enterotomy (21.9 (4.3) kg/m²) ($P < 0.03$). No relationship was found between inadvertent enterotomy and patients' sex, ASA classification, emergency status of the operation, level of surgical experience, and the time between reoperation and the previous laparotomy. The occurrence of inadvertent enterotomy was not related to the indications for operation (Table 1).

Logistic regression analysis revealed that age and the number of previous laparotomies appeared to be associated with the occurrence of inadvertent enterotomy, whereas BMI was not. The odds ratio (95 per cent confidence interval) for the increase in risk with age was 1.9 (1.3–2.7). Three or more previous laparotomies resulted in a more than

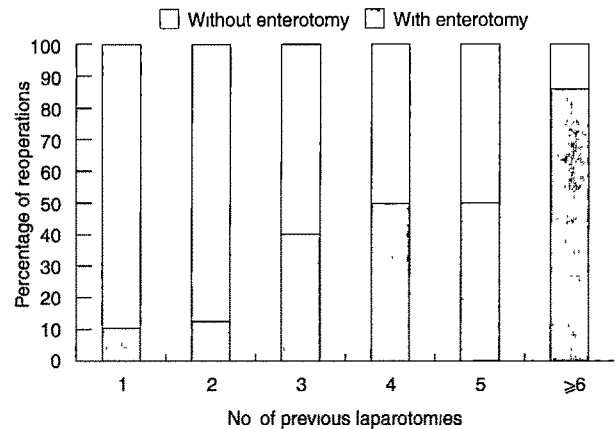


Fig. 1 Relation between the percentage of reoperations with and without enterotomy and the number of previous laparotomies. Odds ratios (95 per cent confidence interval) for the increased risk of enterotomy are 1.6 (0.6–4.0), 7.7 (2.8–21.2), 14.2 (3.8–53.1), 15.8 (3.1–79.7) and 165.7 (14.8–1857.6) for two, three, four, five and six or more laparotomies respectively.

tenfold increased risk of enterotomy compared with one or two laparotomies (odds ratio 10.4 (5.0–21.6)) ($P < 0.001$).

Twenty-three patients died during the hospital stay, seven (13 per cent) of 52 patients with inadvertent enterotomy and 16 (7 per cent) of 218 patients without ($P = 0.18$). As expected, the mortality rate was high among patients with metastatic colonic cancer, other abdominal malignancy and those who had undergone emergency surgery for abdominal aneurysm, while none of the patients with Crohn's disease or ulcerative colitis died.

Patients with enterotomy had significantly more postoperative complications (such as bowel obstruction, anastomotic leak, wound dehiscence, sepsis and pneumonia) than those without enterotomy (28 (54 per cent) of 52 *versus* 76 (35 per cent) of 218; $P < 0.01$), underwent urgent relaparotomy more often (17 (33 per cent) of 52 *versus* 28 (13 per cent) of 218; $P < 0.001$), were admitted to the ICU more often (17 (33 per cent) of 52 *versus* 30 (14 per cent) of 218; $P < 0.001$) and had parenteral nutrition more frequently (19 (37 per cent) of 52 *versus* 31 (14 per cent) of 218; $P < 0.001$). ASA score and BMI did not differ significantly between patients with or without postoperative morbidity.

Median postoperative hospital stay was significantly longer in patients with inadvertent enterotomy (13 (range 5–117) days) than in those without enterotomy (10 (range 2–173) days) ($P < 0.001$).

Discussion

In this study risk factors and the magnitude of complications associated with inadvertent enterotomy following division

of intra-abdominal adhesions were assessed in patients undergoing reoperation.

Underestimating the clinical consequences of inadvertent enterotomy and inability to prevent adhesions effectively are two main reasons why adhesion-related disorders have rarely been addressed in the past. In the recent literature, inadvertent enterotomy has been reported mainly as a complication of laparoscopic surgery^{9,10}, but incidences and consequences are not well documented and a causal relationship with intra-abdominal adhesions is not established. Bowel injuries often occur as a result of injudicious introduction of a trocar or Veress needle¹².

Approximately one in five patients who were reoperated on suffered one or more inadvertent enterotomies. The 19 per cent prevalence is not a completely accurate reflection of the occurrence of this complication, since patients who had previous abdominal surgery but underwent laparotomy via another incision were excluded from this study. Such patients are unlikely to have adhesions under the new incision so including them would have lowered the prevalence. However, because fewer adhesions would be expected under a new incision, less emphasis might be placed on a slow, meticulous and trauma-free entrance to the abdomen in comparison to re-entering the abdomen through a previous incision, resulting in an even higher incidence of inadvertent enterotomy.

The age of the patient and the number of previous laparotomies were independent risk factors for an inadvertent enterotomy. Age-related alterations in the strength and collagen content of the left colon in rats have been described, suggesting an increased risk of bowel injury with age^{13,14}. Similar changes were found in the left colon of humans in necropsy studies¹⁵. Unfortunately, the effect of age on the mechanical strength of the small intestine, the predominant site of inadvertent enterotomy, was not determined. In a recent experimental study of anastomotic healing, collagen production capacity, particularly in the ileum, was found to be suppressed in old rats¹⁶. This may indicate, but does not necessarily imply, an increased risk of enterotomy.

Each additional laparotomy introduces *de novo* adhesions and adhesion reformation, expanding the area of intra-abdominal adhesions. Adhesion reformation is very common after adhesiolysis, even when done laparoscopically^{17,18}. Reformed adhesions seem to be more severe than *de novo* adhesions and the risk of enterotomy is enhanced when they are dissected. Holmdahl *et al.*^{19,20} found increased levels of transforming growth factor (TGF) β and plasminogen activator inhibitor (PAI) type 1 and decreased tissue plasminogen activator activity in human adhesion tissue in comparison to unaffected peritoneum, suggesting an enhanced propensity in areas of adhesiolysis to reform (more dense) adhesions. TGF- β , in particular,

strongly depresses fibrinolytic activity by stimulating PAI-1 production, and induces tissue fibrosis²¹. Whether the total intra-abdominal surface covered by adhesions was greater or the adhesion density was increased when more laparotomies were done could not be assessed accurately from the retrospective data.

It is surprising that the time interval between the index operation and the previous laparotomy was not a risk factor. From experience with 'open abdomen' treatment and delayed abdominal wall reconstruction it is known that adhesions become more 'friendly' with time²². Reports on complications of Hartmann's reversal support this reduction in adhesion density with time²³.

Most enterotomies occurred after the peritoneal cavity was completely opened, when dissecting relevant intra-abdominal adhesions between adherent loops of bowel. Similarly it was calculated that the time needed to divide significant intra-abdominal adhesions was two- to threefold higher than the incision time (time taken from skin incision to complete opening of the abdomen)⁸. Dissecting pelvic adhesions, in particular, frequently caused bowel injury. Presumably, the narrow space hampers gentle adhesiolysis in circumstances in which bowel loops are deeply retracted downwards by adhesive bands. Such pelvic adhesions also appeared to be a major cause of bowel obstruction after colorectal surgery²⁴.

Inadvertent enterotomy led to extension of the surgical procedure with extra bowel resections and/or suturing and probably resulted in more postoperative complications, more (troublesome) re-explorations, a higher rate of ICU admissions, more parenteral nutrition usage and a longer hospital stay. Concomitant medical disease, as reflected by the ASA score, and BMI seemed to be minor risk factors for postoperative morbidity in comparison to inadvertent enterotomy, but the analysis was not multivariate.

In concert with a significant postoperative mortality rate, the clinical impact of inadvertent enterotomy during reoperation seems enormous and most probably matches that of adhesion-related small bowel obstruction⁴. With the advancing age of the population and improvement in medical care, an increase in reoperations is to be expected, thus increasing the incidence of this adhesion-related problem²⁵. Both the clinical and almost certainly the economic impact of adhesiolysis-related inadvertent enterotomy warrant a thorough evaluation of measures preventing adhesions. This study has contributed by identifying risk groups that may benefit most from prevention.

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Audit of time to emergency trauma laparotomy

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Background: An analysis of the process of care may improve quality of care within a trauma system. Early operative control of haemorrhage is vital and any delay before surgery may adversely affect outcome.

Methods: Times from activation of the aeromedical team to arrival in the emergency department and the operating room for patients with liver or spleen injury were analysed to identify factors that delayed laparotomy. These results were compared with those of a national database.

Results: The median time from emergency call to operation was 127 min (140 min for blunt and 86 min for penetrating injuries). Time from arrival in the emergency department to the operating room was 54 min (56 min for blunt and 37 min for penetrating injuries). An audit filter, set at the upper quartile of the emergency call to operating room time, selected 21 patients whose records were examined; five correctable delays were identified. Compared with the national trauma database, these patients had longer on-scene times, but significantly shorter times to operation from the emergency call (127 *versus* 161 min) and arrival at the emergency department (54 *versus* 115 min), although the patients were more severely injured (median Injury Severity Score 34 *versus* 24).

Conclusion: The time to emergency trauma laparotomy may be used effectively as an audit of process for the clinical governance of a trauma system.

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Introduction

Quality assurance and improvement programmes that analyse the provision of trauma care to injured patients have tended to utilize mortality, and to a lesser extent morbidity and disability, as markers of effectiveness. While these outcome measures are important and powerful indicators of the capability and efficacy of a trauma system, they have significant limitations. For a trauma system that manages patients from the moment of injury through to discharge from rehabilitation services, these distant end-points provide little information about the process of care that is delivered. Many factors are involved in determining the final outcome of a trauma patient. Management decisions that have clinically important consequences may become hidden among the myriad of other interventions that occur during multidisciplinary care. While outcome measures may identify the presence of deficiencies within a particular trauma system, it may be difficult to identify the

points at which these deficiencies lie. It therefore becomes impossible to implement change and so neither quality assurance nor quality improvement is achieved.

Trauma audit can be made easier and more effective by an analysis of the process of care. By focusing the audit in this way the study becomes more directed and deficiencies in the system are more apparent. Improving one aspect of a system may lead to improvements in other areas. As an example, it is known that evacuation of an extradural haematoma is a time-dependent procedure¹. If carried out within 4 h of injury there is a significant improvement in survival and disability. An audit of 'time to extradural evacuation' might identify and then correct a problem with access to computed tomography (CT). A subsequent improvement in the care of other patients with injuries requiring CT may also be seen.

An ideal audit tool is clinically relevant and important, related to outcome, easy to measure and to apply. It should be able to identify deficiencies in management on a local level and allow comparisons to be made against regional or

national norms. This study was undertaken to determine whether the time to emergency surgery for intraperitoneal solid organ injury qualifies as a tool for audit of the trauma process.

Patients and methods

The Helicopter Emergency Medical Service² subset of the trauma database of the Royal London Hospital (RLH) was used for the local audit. This is an integrated system of prehospital and in-hospital trauma care. These patients were not duplicated in the United Kingdom Trauma Audit and Research Network (UK-TARN)^{3,4}, the standard national trauma database for the study (previously the Major Trauma Outcome Study – UK).

The records for all patients injured between January 1991 and May 1996 were examined. The inclusion criteria were a liver or spleen injury with an Abbreviated Injury Score (AIS)⁵ of 2 or more and laparotomy performed within 8 h of injury. The 8-h limit was taken to include delays and early failure of non-operative management but to exclude surgery for late complications in the patients' clinical course. Patients transferred to another hospital for surgery were excluded.

Data were collected on patient demographics, mechanism of injury, Injury Severity Score (ISS)⁶, time of the initial emergency call, arrival time in the emergency department and time of arrival in the operating room. The initial emergency call time was as near to the injury time as was available. It was not possible to collect comparable physiological data. The UK-TARN database does not record prehospital physiological data and the RLH patients receive more resuscitation and interventions in the prehospital phase of their management, so making comparisons of emergency department figures meaningless.

RLH patients for review were identified as those with a time from arrival in the emergency department to reaching the operating room of over 50 min for penetrating injury and 100 min for blunt injury. These patients were in the upper quartile of the distribution of this period and may have experienced unnecessary delay in their process of care.

The RLH times were then compared with those of the national UK-TARN database. Data were processed using Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) and Arcus Quickstat Biomedical (Longman Software, Cambridge, UK) software packages. For both patient groups the proportion of patients with penetrating trauma and isolated abdominal trauma was calculated and subjected to χ^2 analysis. Medians and interquartile ranges for ISS, the time between the emergency call and arrival at the operating room, and the time from arrival at the emergency department to arrival at the

operating room were calculated, and the distributions compared using the Mann–Whitney *U* test. ISS, mechanism of injury and trauma system (RLH or UK-TARN) were examined in a multiple regression analysis. $P < 0.05$ was used to define statistical significance.

Results

The characteristics of the patients from the RLH and UK-TARN databases are shown in Table 1. There was no significant difference in age or sex distribution between the two groups. A significantly greater proportion of RLH patients had abdominal AIS scores of 2 or more and proceeded to laparotomy within 8 h of emergency room arrival ($P < 0.001$, χ^2 test). In addition they had a higher ISS (median 34 *versus* 24; $P < 0.001$) and were less likely to have an isolated abdominal injury (6 *versus* 67 per cent; $P < 0.001$). The proportion of patients sustaining penetrating trauma was similar.

The median time from the emergency call to arrival in the operating room was 127 min for the RLH patients. This was subdivided into 140 min for blunt and 86 min for penetrating injuries (Table 2). Overall, the median time from arrival in the emergency department to operation was 54 min; 56 min for blunt trauma and 37 min for penetrating (Table 3).

Patients with emergency call to operating room times over the third quartile had their case records reviewed. This audit filter level identified 16 patients with blunt trauma and five with penetrating injuries. These patients had delays identified in either their prehospital or in-hospital management. In the prehospital phase, unavoidable delays were due to entrapment and prolonged extrication. Avoidable delays were usually attributed to late activation of the helicopter by the dispatch system but there was one patient with an inappropriately long on-scene time.

Table 1 Study population

	RLH	UK-TARN
No. of patients	1617	51 408
Study group*	86 (5)	533 (1)
999 time recorded*	86 (100)	148 (28)
Sex ratio (M : F)	2.9 : 1	3.2 : 1
Age (years)†	30 (22–49)	26 (19–44)
ISS†	34 (17–46)	24 (13–34)
Isolated abdominal injury*	5 (6)	357 (67)
Penetrating injury*	21 (24)	100 (19)
On-scene time (min)†	62 (50–80)	46 (35–70)

*Values in parentheses are percentages, †values are median (interquartile range) RLH, Royal London Hospital; UK-TARN, United Kingdom Trauma Audit and Research Network; ISS, Injury Severity Score

Table 2 Time from emergency call to operation

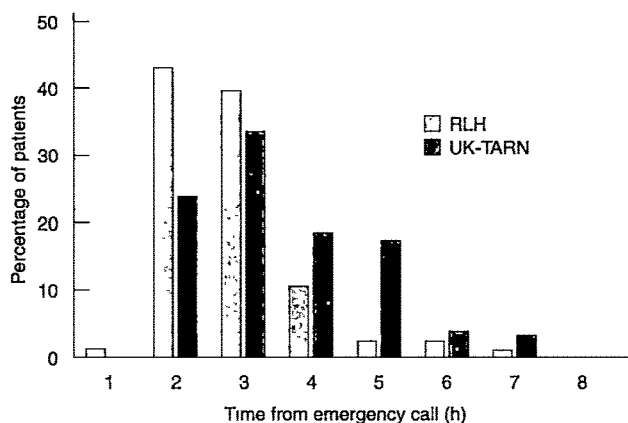
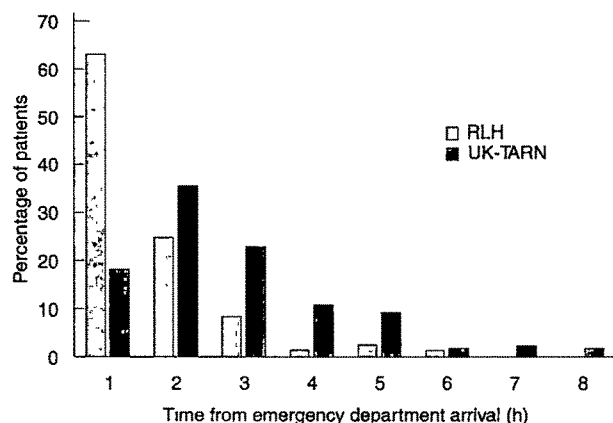
	All		Blunt		Penetrating	
	RLH (n=86)	UK-TARN (n=148)	RLH (n=65)	UK-TARN (n=127)	RLH (n=21)	UK-TARN (n=21)
Emergency call to operation (min)	127 (94–163)	161 (124–245)*	140 (111–173)	169 (128–252)*	86 (78–118)	135 (90–212)†

Values are median (interquartile range). RLH, Royal London Hospital, UK-TARN, United Kingdom Trauma Audit and Research Network * $P < 0.001$, † $P = 0.011$ versus RLH (Mann-Whitney U test)

Table 3 Time from emergency department arrival to operation

	All		Blunt		Penetrating	
	RLH (n=86)	UK-TARN (n=533)	RLH (n=65)	UK-TARN (n=433)	RLH (n=21)	UK-TARN (n=100)
Emergency department arrival to operation (min)	54 (37–88)	115 (73–180)*	56 (41–102)	123 (78–197)*	37 (29–51)	115 (73–180)*

Values are median (interquartile range) RLH, Royal London Hospital, UK-TARN, United Kingdom Trauma Audit and Research Network. * $P < 0.001$ versus RLH (Mann-Whitney U test)

**Fig. 1** Time to operation from emergency call. RLH, Royal London Hospital; UK-TARN, United Kingdom Trauma Audit and Research Network**Fig. 2** Time to operation from arrival in the emergency department. RLH, Royal London Hospital; UK-TARN, United Kingdom Trauma Audit and Research Network

In hospital, some patients with an identified intraperitoneal injury went on to laparotomy after failure of non-operative management. Patients in a second group were haemodynamically stable and would normally qualify for non-operative management but for the presence of significant multiple injuries. In these patients, laparotomy was carried out after treatment of the higher priority injuries. However, five patients were identified in whom the clinical decision to proceed to the operating room was delayed incorrectly, either by prolonged resuscitation or by

inappropriate investigations (CT). There were data collection errors relating to two additional patients identified by the audit filter, who did not fall into the delayed surgery category.

The local RLH data were then compared with the national UK-TARN data. The time of the call to the emergency services was available for only 28 per cent of these patients. RLH patients spent a median of 16 min more time on scene than the those in the national data set ($P < 0.001$). Overall, the UK-TARN patients had a median

time to operation from emergency call of 161 min, 34 min longer than that of the RLH patients. Patients with blunt trauma spent 29 min longer in the preoperative phase and victims of penetrating trauma 49 min longer. All these differences were statistically significant. *Fig. 1* shows the distribution of times for patients to proceed to laparotomy from the time of emergency call.

With respect to the times from emergency department arrival to operation, the RLH patients also proceeded to laparotomy significantly faster. Overall, UK-TARN patients arrived in theatre 61 min after the RLH patients (median values), 67 min for blunt and 78 min for penetrating injury. *Fig. 2* shows the distribution of times for patients to proceed to laparotomy from the time of arrival in the emergency department.

The interrelationship between ISS, penetrating injury and trauma system effect was examined in a multiple regression analysis. All three factors proved highly significant ($P < 0.001$). Patients with a high ISS, penetrating trauma and RLH patients were more likely to arrive in the operating room faster than other patient groups. This indicates that the trauma system effect was independent of injury severity and mechanism.

Discussion

This study evaluated the use of 'time to emergency trauma laparotomy' as an audit tool for the process of trauma care. There is an underlying assumption within an audit of process that the activities under review have previously been shown to have a beneficial outcome. It is known that timely arrest of uncontrolled haemorrhage is clinically relevant and important. In the Advanced Trauma Life Support Program of the American College of Surgeons, only oxygenation and ventilation manoeuvres take precedence⁷. Ongoing haemorrhage and increasing blood product administration are known to affect survival adversely⁸ and increase the incidence of multiple organ failure⁹, systemic inflammatory response syndrome and acute respiratory distress syndrome¹⁰.

The three time variables of emergency call, emergency department arrival and operating room time are easy to measure, and readily available from prehospital and in-hospital records. This study shows that it is possible to collect and analyse these data on both a local and national basis. Using these times it was possible to identify a subset of patients for case review, and potential problems with the system were highlighted for further study and action.

Time to emergency trauma laparotomy therefore fulfils the criteria necessary of a tool for auditing the process of trauma care. It can be applied to assess efficiency and performance of both a trauma system (time from injury to

surgery) and an individual institution (time from emergency department arrival to surgery).

Whether the time from injury or from hospital arrival should be used is open to question. In-hospital audit will focus on the time from emergency department arrival to operation. Nationally, a median of 46 min will already have elapsed after the injury occurred. From the patients' perspective, the time from injury must be the most relevant and is a better measure of the overall process of care. The small number of patients whose time of injury was available from the UK-TARN database reflects the lack of medical control or interest in the prehospital arena.

Prehospital and in-hospital care are integrated in the RLH trauma system. Patients receive many of their initial critical interventions in the prehospital phase of their management with most necessary airway and ventilation procedures carried out at the scene. While prolonging the time at the scene, this will result in emergency department to laparotomy times that systems without advanced prehospital medical care are unlikely to be able to achieve. However, even when considering the whole period from injury to laparotomy, the RLH patients arrived in the operating room 34 min faster than the national average, even though the patients had more severe injuries and more multisystem trauma.

While it is well known that control of haemorrhage is important, and therefore time to emergency laparotomy may be a useful performance indicator, there is inadequate scientific evidence to determine at which level to set the audit filter. This would represent a limit for the time to operation, over which the details of a case should be reviewed. Without a scientific limit, it is appropriate to choose a filter that selects a certain proportion of the patients, perhaps a number that can feasibly be reviewed adequately in an audit meeting. Selecting the upper quartile for the UK-TARN database would choose patients with a time from arrival at the emergency department to operation of over 200 min for blunt trauma and 180 min for penetrating trauma. These values may be used as a guide for trauma audit in other hospitals. However, a delay to laparotomy of over 2 h, as used by the American College of Surgeons¹¹, has been shown to affect outcome adversely¹².

This method will identify patients who have experienced excessively long delays; however, it will miss those who have a laparotomy within this timespan, but should have been in the operating room much sooner. For example, 3 h from emergency department to operation would be unacceptable in a haemodynamically unstable patient with an abdominal stab wound. Conversely, for individual patients, surgery beyond these times may be entirely appropriate. Case-note review may reveal a failure of non-operative management of a liver or spleen injury. None the less, review of these cases is

important, if only to discuss the validity of the original treatment decision.

There are wide discrepancies and variations in the provision of trauma care across the UK. In the UK, all hospitals with an emergency department can receive victims of major trauma. Participation in the UK-TARN is voluntary and quality assurance is not a requirement for verification, as it is in the USA, despite a national recommendation by the Royal College of Surgeons in 1988¹³. Every doctor is required to participate in medical audit¹⁴ and all doctors involved in trauma management have a duty of care to the injured patient. Audit of the process of care is a practical and useful tool for clinical governance within trauma services. Time to emergency laparotomy for intraperitoneal solid organ injury fulfils the criteria of an audit tool to be used as part of a quality improvement programme.

Acknowledgements

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Belching and bloating: facts and fantasy after antireflux surgery

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Background: Fundoplication is commonly complicated by belching difficulty and abdominal bloating. Postoperative belching ability, however, is difficult to assess; subjective patient reporting is often used but may be unreliable. Manometric measurement of the gastro-oesophageal 'common cavity' is an objective marker of gastro-oesophageal gas reflux.

Methods: Twenty patients who had undergone Nissen fundoplication and 11 healthy controls underwent oesophageal manometry at rest and during gastric distension for 10 min with 750 ml of gas.

Results: Half of the patients reported an inability to belch; the other half reported varying degrees of belching difficulty, most of whom were rarely able to relieve bloating by belching. During gastric distension, none of the patients had transient lower oesophageal sphincter relaxation, while the controls had a median of 1 (range 0–1). Patients had fewer common cavities than controls; however, none of the belch urges experienced during gastric distension in patients was associated with a common cavity, compared with 48 per cent in controls.

Conclusion: After fundoplication, patients do not belch as a result of gastro-oesophageal gas reflux; rather it may be due to oesophagopharyngeal reflux of swallowed air. Subjective reporting of belching ability is inaccurate and manometric measurement of common cavities provides a better means of assessment.

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Introduction

While producing effective control of gastro-oesophageal reflux, antireflux surgery is often complicated by abdominal distension, the so-called 'gas bloat' syndrome, due to disturbed belching function. However, there is much variation in the reported incidence of bloating and associated problems following fundoplication. Reported ranges are 1.5–100 per cent of patients unable to belch, 31–63 per cent unable to vomit and 13–67 per cent complaining of gas bloating^{1–13}.

Belching is initiated by distension of the cardia, producing transient lower oesophageal sphincter (LOS) relaxation, such that air escapes into the oesophagus, and the pressure between the stomach and oesophagus equalizes, the so-called 'common cavity' phenomenon¹⁴. Oesophageal distension then produces either secondary peristalsis, such that the air is swept back into the stomach, or upper oesophageal sphincter relaxation,

leading to oesophagopharyngeal gas reflux and an audible belch. The development of a gastro-oesophageal common cavity can therefore be used as a manometric marker of gastro-oesophageal gas reflux and may be associated with the urge to belch¹⁴.

Fundoplication renders LOS relaxation incomplete^{15,16}, which may lead to disturbance of belching. However, accurate assessment of postoperative belching ability can be difficult. Most reports of belching difficulties after fundoplication are based on subjective assessment rather than objective measurement. Belch volumes have been measured in an attempt to assess belching difficulties objectively, but no relation between belch volume and the degree of belching difficulty was found¹⁷. The gastro-oesophageal common cavity provides a manometric marker of gastro-oesophageal gas reflux. The aim of this study therefore was to compare subjective assessment of the ability to belch with objective measurement of gastro-oesophageal common cavity phenomena.

Patients and methods

Patients

This study was approved by the Research Ethics Committee of the Royal Adelaide Hospital and all subjects gave written informed consent. Twenty patients who had previously undergone Nissen fundoplication and 11 age-matched healthy asymptomatic controls were studied. Exclusion criteria included previous oesophageal or gastric surgery before the fundoplication, primary connective tissue disease, significant central nervous system or cardiac disease, diabetes mellitus or medication that could affect oesophageal motility, such as anticholinergics, tricyclic antidepressants, neuroleptics and prokinetic agents, that could not be stopped for at least 48 h before the study.

Before operation all patients had typical symptoms of gastro-oesophageal reflux; 12 patients had endoscopic evidence of erosive or ulcerative oesophagitis, a further four had oesophageal acid exposure greater than 6 per cent of the time on 24-h pH monitoring, and another patient had a positive Bernstein test and positive standard acid reflux test during oesophageal manometry. No preoperative testing information was available on the remaining three patients.

Operative technique

Surgery was performed laparoscopically in 19 patients and by open operation in one (during the transition period of changing from open to laparoscopic surgery). The fundoplication was performed over a 52-Fr bougie in 15 patients, a 50-Fr bougie in one, a 46-Fr bougie in one patient and no bougie in the remaining three, according to surgeon preference. The technique has been reported in detail elsewhere¹⁸.

Belch scores

Using a preplanned questionnaire, subjects were interviewed regarding their own assessment of their ability to belch, to relieve bloating by belching and to vomit. Other symptoms such as nausea, periprandial abdominal pain, ability to eat a normal size meal and flatulence were also recorded.

Oesophageal manometry

Subjects underwent oesophageal manometry, between 3 and 12 months after operation in the patient group, using a multilumen manometric assembly that incorporated a

sleeve sensor to record LOS pressure¹⁹. A side hole at the distal margin of the sleeve recorded intragastric pressure. Five side holes, 4 cm apart starting at the proximal sleeve margin, recorded oesophageal body motility, and a side hole in the pharynx monitored swallowing. The central core was used as a gastric infusion channel. The sleeve, gastric and oesophageal lumens were perfused at 0.6 ml/min by a low-compliance pneumohydraulic capillary infusion pump (Arndorfer Medical Specialities, Greendale, Wisconsin, USA); the pharyngeal side hole was perfused at 0.3 ml/min. Each lumen was connected to an external transducer (Statham P23D; Gould, Oxnard, California, USA), with output displayed on a multichannel chart recorder (Model 7D; Grass, Quincy, Massachusetts, USA).

Protocol

Subjects were instructed to fast for 6 h, and anticholinergic, antisecretory and antidopaminergic medication was stopped 48 h before the study. The manometric assembly was passed via the nose and positioned such that the sleeve straddled the LOS¹⁹. It was then left in place for 10–15 min to allow patient accommodation before any readings were taken.

The subject was seated upright and asked to indicate the urge to belch with a hand-held event marker. After a 10-min baseline recording, the stomach was distended with 750 ml carbon dioxide. This was generated in the stomach by the instillation, over 10 s via the core of the manometric assembly, of 15 ml Field's Negative C (Fields Group Chemicals, Sydney, Australia), a mixture of a food-grade acid and an alkali-metal bicarbonate. Manometric measurements and belch urges were recorded for a further 10 min. Although this technique represented an artificial situation, a certain amount of gastric distension was necessary to induce LOS relaxations if these were going to occur.

Data analysis

Basal LOS pressure was measured at end-expiration and referenced to intragastric pressure. Visual readings were taken every minute, from which the mean value for the whole 10-min period was calculated. LOS relaxation was deemed to have occurred if the sphincter pressure decreased by at least 5 mmHg in less than 5 s and lasted a minimum of 5 s²⁰, and was measured as the residual pressure at maximal relaxation.

The chart recordings were analysed manually for the number of spontaneous transient LOS relaxations and belch urges with or without common cavities during both the 10-min rest period and in the 10 min after distension. A transient LOS relaxation was defined as an abrupt fall in

LOS pressure, at a rate of more than 1 mmHg/s to within 2 mmHg of swallow-induced LOS relaxation¹⁴, not associated with a swallow signal, and was scored if the nadir pressure during relaxation was equal to or less than the nadir pressure determined during water swallows¹⁶. A common cavity episode was defined as an abrupt increase in intraoesophageal body pressure to intragastric pressure in at least two lower oesophageal body manometric recording sites, and was accepted as a marker of gas or liquid reflux from the stomach to the oesophagus¹⁴.

Statistical analysis

Data were analysed by Mann-Whitney *U* test for non-parametric data, using the SPSS for Windows (version 6.0) program (SPSS, Chicago, Illinois, USA), with statistical significance set at $P < 0.05$.

Results

The patient and control groups were demographically similar, with no significant age difference (median (range) 45 (23–65) *versus* 42 (20–53) years respectively; $P < 0.05$), although the male:female ratio was different (7:13 *versus* 7:4). Based on the questionnaire findings, half of the patients were unable to belch. The other half reported varying degrees of difficulty with belching, but the majority of those who could belch were rarely able to relieve bloating by belching (Table 1). No patient had dysphagia of note.

During both rest and gastric distension, the patients had no transient LOS relaxations. In contrast, the controls had none at rest and a median of 1 (range 0–1) during gastric distension ($P < 0.05$).

At rest, the median number of common cavities was similar in patients and healthy controls, and there was no significant difference between the groups in the total number of belch urges, belch urges without common cavities or belch urges with common cavities. At rest, the proportion of belch urges associated with a common cavity was equally low in patients and controls (Table 2).

During gastric distension, the median number of common cavities was less in patients than healthy controls ($P < 0.05$). There was no significant difference between patients and controls in either the total number of belch urges or belch urges without common cavities. However, in contrast to controls ($P < 0.05$), no patient had a common cavity associated with a belch urge. During gastric distension, none of the belch urges was associated with a common cavity in the patients compared with 48 per cent in the controls ($P < 0.05$) (Table 2).

Table 1 Belching ability and ability to relieve bloating by belching

	Score	No. of patients
Belching ability		
Normal	0	1
Can belch sometimes	1	7
Can belch with difficulty	2	2
Unable to belch at all	3	10
Ability to relieve bloating by belching		
Complete relief	0	0
Relief sometimes possible	1	3
Relief rarely possible	2	7
No relief at all	3	10

Table 2 Comparison of common cavities and belch urges at rest and during gastric distension in patients after fundoplication and in healthy controls

	Patients after fundoplication	Healthy controls
Rest		
Common cavities	0 (0–1)	0 (0–4)
Belch urges (total)	0 (0–12)	0 (0–5)
Belch urges without common cavities	0 (0–12)	0 (0–5)
Belch urges with common cavities	0 (0–1)	0 (0)
Belch urges with common cavities (%)	3	0
Gastric distension		
Common cavities	0 (0–1)*	2 (0–7)
Belch urges (total)	1 (0–13)	4 (0–8)
Belch urges without common cavities	1 (0–13)	2 (0–7)
Belch urges with common cavities	0 (0)*	1 (0–4)
Belch urges with common cavities (%)	0*	48

Values are median (range). * $P < 0.05$ *versus* healthy controls

Discussion

Previous studies have reported that between 43 and 80 per cent of patients are able to belch after total fundoplication^{4,8}. Other studies have reported that patients with partial fundoplication also retain the ability to belch and have no postprandial bloating or increased flatus^{4,5,21,22}. These studies, however, have relied on subjective accounts of belching ability^{1–13}. In the present study, an objective measure of gas reflux was used as well as the subjective marker of belch urge to assess the ability of patients to belch after total fundoplication. Contrary to previous reports, while many patients reported the ability to belch and to relieve bloating by belching, these subjective assessments did not correlate with objective measures of gas reflux.

Following fundoplication, patients exhibited no transient LOS relaxations and almost no oesophageal common cavities, suggesting that the mechanism of belching in such patients is different from that in controls.

In normal circumstances, belching is associated with gastro-oesophageal gas reflux followed by oesophagopharyngeal gas reflux. Usually, reflux of gas occurs during transient LOS relaxation¹⁴. A gastro-oesophageal common cavity is an objective marker of gastro-oesophageal gas reflux. Cineradiographic studies have confirmed that gastro-oesophageal common cavities occur concurrently with oesophageal distension caused by gas reflux²³. This distension is usually the factor leading to the perception of an urge to belch. As in previous studies²⁴, fundoplication substantially reduced the number of transient LOS relaxations and virtually eliminated the occurrence of gastro-oesophageal common cavities. However, fundoplication did not reduce the frequency of belch urge, and belch urges after fundoplication were not associated with objective evidence of gas reflux, whereas this association was common in the controls.

The mechanism of belching in patients following fundoplication remains to be determined. However, it is likely that the belching is of swallowed air that has been retained in the oesophagus because of failed peristalsis. This suggestion is consistent with previous studies which have shown that upper oesophageal sphincter relaxation and oesophagopharyngeal venting of gas can occur voluntarily and independently of LOS relaxation²⁵.

It has been suggested that impaired belching and aerophagia may accentuate meteorism^{26,27}. A widely accepted explanation is that swallowed air is trapped in the fundus and cannot be released through the one-way valve of the fundoplication¹. An inability to belch is associated with increasing flatus, and gas bloat may be relieved by dilatation of the gastro-oesophageal junction²⁸. In the present study, subjective accounts of the ability to belch and relieve bloating by belching did not correlate with the number of belch urges or objective evidence of belching. Therefore, the patients' perception of their ability to belch may not be a reliable measure of surgical outcome.

In conclusion, patients do not experience gastro-oesophageal gas reflux after fundoplication, as their belches are not associated with the formation of gastro-oesophageal common cavities. Although they may report the ability to belch, belches in these patients may be the result of eructation of swallowed oesophageal gas. Hence, subjective reporting may be an inadequate method of assessing true belching ability following fundoplication. Manometric assessment of common cavities provides a more accurate assessment of belching ability and should be used to compare the outcome of different antireflux operations.

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Laparoscopic needle catheter jejunostomy

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Introduction

A feeding jejunostomy is commonly placed prophylactically after major upper gastrointestinal operations and in patients who require prolonged enteral feeding. Different techniques to accomplish laparoscopic jejunostomy have been reported ranging from laparoscopically assisted jejunostomy¹ to the use of T-fasteners² or transabdominal suturing techniques³. Open needle catheter jejunostomy has been reported by Myers *et al.*⁴ (222 consecutive applications) and Sarr⁵ (500 consecutive applications) to be safe and to have a low complication rate. However, there has been only one case report of laparoscopic needle catheter jejunostomy placement⁶. This study reports preliminary results of a laparoscopic needle catheter jejunostomy placed using a total intracorporeal suturing technique.

Patients and methods

From August 1996 to August 1999, 66 patients (28 women and 38 men; mean age 63 (range 23–89) years) underwent laparoscopic feeding jejunostomy. Fifty-eight feeding jejunostomy tubes were placed in conjunction with another procedure; eight jejunostomy tubes were placed as the primary procedure (*Table 1*). Two types of catheter were placed: a 10-Fr silastic catheter using a peel away sheath introducer was placed in five patients (Flexiflo Lap-J tube; Ross Laboratories, Columbus, Ohio, USA) and a needle catheter jejunostomy (Compat; Novartis Nutrition Corporation, Minneapolis, Minnesota, USA) was placed in 61.

Laparoscopic jejunostomy was performed with the use of three abdominal trocars. In patients undergoing minimally invasive oesophagectomy, the abdominal trocars were the same as those used for the oesophagectomy procedure.

With the patient in a 30° reverse Trendelenburg position, the greater omentum was reflected superiorly over the

Table 1 Indications for laparoscopic placement of a jejunostomy in 66 patients

Indication	No. of patients
Combined thoracoscopic and laparoscopic oesophagectomy	46
Unresectable oesophageal cancer	6
Laparoscopic staging for upper gastrointestinal cancer	5
Oesophageal perforation	4
Laparoscopic Heller myotomy	2
Gastroparesis	2
Gastric perforation requiring laparoscopic repair	1

stomach to expose the transverse mesocolon. The proximal jejunum, 30 cm distal to the ligament of Treitz, was identified and sutured to the left upper quadrant anterior abdominal wall using the Endostitch device (US Surgical Corporation, Norwalk, Connecticut, USA). A 2-mm incision was made on the anterior abdominal wall right above the suspended jejunal limb. An introducer needle was introduced into the peritoneal cavity close to the jejunal loop and inserted into the jejunal lumen. A jejunostomy catheter with its guidewire was introduced through the introducer needle into the efferent limb of the jejunum. The guidewire and introducer needle were removed, leaving the needle catheter in place. A single intracorporeal purse-string suture was placed between the jejunal loop and the anterior abdominal wall to create a seal around the feeding needle catheter (*Figs 1a* and *1b*). A small volume of air (10 ml) was injected into the jejunostomy catheter to confirm the intraluminal position of the feeding catheter. The distal jejunum was anchored to the anterior abdominal wall about 4 cm distal to the insertion site to prevent potential volvulus around a single point of fixation.

Enteral feeding was started 24 h after jejunostomy placement. All jejunostomy catheters placed in patients who underwent oesophagectomy were left in place for a minimum of 3 weeks or until the patient could tolerate adequate oral nutrition. All patients were instructed to flush the tube with 15 ml water every 8 h to prevent clogging of the catheter.

Results

Sixty-six patients underwent laparoscopic placement of a catheter jejunostomy. None of the laparoscopic jejunostomy procedures was converted to an open laparotomy. In the last 15 procedures the mean operative time was 35 min. The jejunostomy tube was used in the immediate post-operative period in all patients. Two of five patients who had a silastic jejunal catheter placed developed localized infection at the insertion site. Two other complications

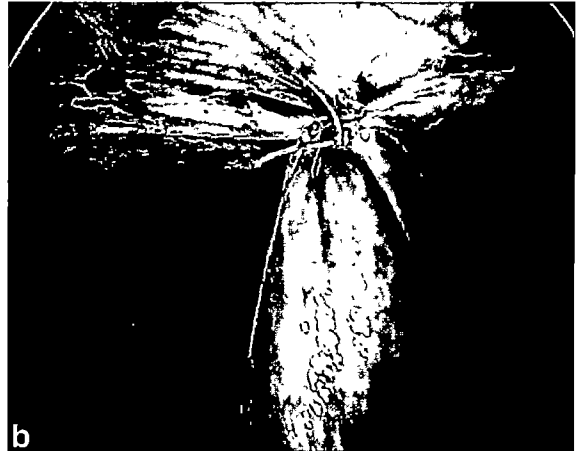
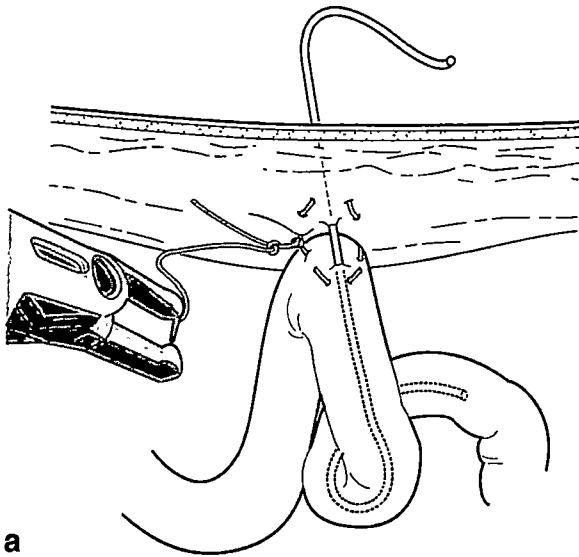


Fig. 1 **a** Schematic view showing the position of the purse-string sutures to create a seal around the jejunal catheter using intracorporeal suturing. **b** Intraoperative photograph showing a jejunal loop following insertion of a needle jejunostomy catheter

occurred after 61 laparoscopic needle catheter jejunostomies: catheter obstruction in one patient and small bowel perforation in another. The patient with catheter obstruction required a second laparoscopic exploration, removal of the clogged catheter and placement of a new catheter after several failed attempts to unclog the first one. The bowel perforation occurred in the early period of the learning curve from traumatic handling of the small bowel. The perforation was repaired initially but the patient was found to have bile drainage from a trocar insertion site on the first day after operation which necessitated immediate laparoscopic re-exploration and resuturing of the perforation site. There were no fatal complications.

Discussion

The two important technical issues in laparoscopic jejunostomy placement are the method for anchoring the jejunal loop to the underside of the anterior abdominal wall and the type of catheter used. Laparoscopic anchoring of the jejunum to the anterior abdominal wall is a difficult task using conventional laparoscopic suturing techniques; the angle of the needle holder in relation to the anterior abdominal wall makes it difficult to place sutures. The Endostitch device was used in this series to facilitate anchoring of the jejunal loop to the underside of the anterior abdominal wall. Intracorporeal suturing obviates the need for transabdominal suturing or the use of T-fasteners^{2,3}. In

the authors' experience, the needle catheter jejunostomy was technically easier to place than the silastic jejunostomy catheter (made specifically for laparoscopic application) that uses a peel away introducer.

In summary, laparoscopic needle catheter jejunostomy is a safe alternative to conventional open needle catheter jejunostomy. The procedure can be performed using intracorporeal suturing without the need for special equipment such as the T-fastener or transabdominal suturing.

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Reliability of sentinel lymph node biopsy for staging melanoma

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Background: The aim of this study was to evaluate the reliability of sentinel lymph node biopsy for staging melanoma.

Methods: Two hundred consecutive patients with a cutaneous melanoma of at least 1.0 mm Breslow thickness, without palpable regional lymph nodes, were included from 1993 in a prospective cohort study in a single tertiary care hospital. One day after lymphoscintigraphy, sentinel node biopsy was performed, guided by a γ probe and patent blue dye. Lymph node dissection was performed only if metastasis was found in a sentinel node. Median follow-up was 32 (range 3–61) months. No patient was lost to follow-up.

Results: A sentinel node was removed in 199 of 200 patients (mean 2.2 nodes per patient). Forty-eight patients (24 per cent) had metastasis in a sentinel node. Fifteen patients developed recurrence after removal of a tumour-negative sentinel node; six relapsed in the previously mapped basin (false-negative rate 11 per cent (six of 54)). The overall survival at 3 years was 93 per cent if the sentinel node was negative and 67 per cent if it was positive. Sentinel node status and Breslow thickness were strong predictors of recurrence and survival. Minor complications were seen in 18 patients.

Conclusion: The sentinel node status was a strong prognostic factor, even with a false-negative rate of 11 per cent.

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Introduction

Sentinel lymph node biopsy is being used increasingly for staging in patients with clinically localized melanoma (American Joint Committee on Cancer stage I–II)^{1–4}. Morton *et al.*¹ used a vital blue dye to trace the node when they introduced the technique in 1992. Alex *et al.*⁵ first described the intraoperative use of a γ ray detection probe. Combining preoperative lymphoscintigraphy, vital dye and γ probe facilitates sentinel node identification and possibly improves the accuracy of staging^{2,6–9}. The sentinel node can thus be identified in 90–100 per cent of patients^{2,10–14}.

When the sentinel node is tumour free and no lymph node dissection is performed, follow-up is needed to confirm that staging with lymphatic mapping was reliable. At present, only three series have been published with a mean follow-up of more than 24 months^{4,15,16}. The present study evaluated accuracy of sentinel node biopsy for staging melanoma, the prognostic value of sentinel node status and

the morbidity associated with the procedure, with mean follow-up of 29 months.

Patients and methods

From October 1993 to October 1998, 200 consecutive patients presenting to The Netherlands Cancer Institute with cutaneous melanoma of at least 1.0 mm Breslow thickness were enrolled in a prospective cohort study to validate the sentinel lymphadenectomy procedure (*Table 1*). Palpable regional lymph nodes, clinical evidence of distant metastases and pregnancy were reasons for exclusion. The study protocol was approved by the Institutional Review Board and informed consent was obtained from all patients.

One day before surgery, lymphoscintigraphy was performed with a dual-head γ camera with low-energy, high-resolution collimators. Some 60 MBq ^{99m}Tc-labelled human albumin colloid (Nanocoll; Amersham Cygne, Eindhoven, The Netherlands) in 0.3 ml was injected

Table 1 Characteristics of patients with a melanoma

	All patients (n=200)
Sex	
Men	93 (46)
Women	107 (54)
Age (years)*	48 (16–78)
Primary tumour location	
Trunk	72 (36)
Leg	82 (41)
Arm	33 (16)
Head/neck	13 (6)
Breslow thickness (mm)*	2.7 (1.0–11.9)
Clark level	
II	9 (5)
III	85 (44)
IV	88 (46)
V	11 (6)
Histology	
Superficial spreading	105 (52)
Nodular	76 (38)
Acrolentiginous	9 (4)
Lentigo maligna	2 (1)
Unclassified	8 (4)
Ulceration	
Present	65 (32)
Absent	135 (68)
Margin of tumour excision before mapping (cm)	
No previous excision	12 (6)
<0.5	166 (83)
0.5–1.9	13 (6)
2.0–3.0	9 (4)

*Values are mean (range). Other values in parentheses are percentages

intradermally around the tumour or biopsy site. Imaging was performed for 30 min after injection and again after 2 h. The location of the sentinel node(s) was indicated on the skin with indelible ink.

All 200 operations were performed by one of two surgeons. After induction of general anaesthesia, 1.0 ml patent blue dye (Bleu Patenté V; Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected intradermally, completely surrounding the tumour or biopsy site. Through a small incision, blue-stained lymphatic vessels were sought and followed up to the site at which they drained into a lymph node. A γ ray detection probe (Neoprobe 1000/1500; Neoprobe Corporation, Dublin, Ohio, USA) was used to confirm that a blue node was radioactive. If no blue-stained lymphatic vessels were found, the probe was used to guide the dissection.

A lymph node was considered to be a sentinel node when a blue afferent lymphatic vessel was identified coming from the injection site and leading to this node. If no blue dye was seen during exploration, nodes that had a separate afferent lymphatic vessel on lymphoscintigraphy were sought. If no

lymphatic vessel was visualized with either blue dye or scintigraphy, the first hot spot in each basin that appeared on the lymphoscintigraphy images was regarded as the sentinel node.

Microscopic sections were cut at 100- μ m intervals at six levels for sentinel nodes smaller than 1 cm, and at three levels per 0.2 cm for larger nodes. Sections were stained with haematoxylin and eosin, and immunohistochemically (S-100 and HMB-45, which are melanoma cell-specific surface proteins). Lymph node dissection was performed only if metastasis was found in a sentinel node.

Median follow-up was 32 (range 3–61) months. Almost all patients were followed in outpatients at the treating hospital, at 3-month intervals in the first year, decreasing to one visit per year after 5 years. Physical examination was performed at each visit. Specific diagnostic tests were performed when indicated. No patient was lost to follow-up.

Statistical analysis

Logistic regression analysis was used to identify factors predicting a positive sentinel node. Disease-free and overall survival curves were constructed by the Kaplan–Meier method. Multiple regression analysis was performed with the Cox proportional hazard model. Variables to be entered into the regression analyses were chosen on the basis of the results of previous studies. The model selected for regression was created by the backward stepwise elimination method.

All statistical analyses were performed with Statistical Package for the Social Sciences software (SPSS, Chicago, Illinois, USA).

Results

Sentinel node identification

A sentinel node was identified in all patients. In one patient the sentinel node was not harvested because it was located centrally in the parotid gland. This was early in the study and the site was deliberately not explored to avoid the risk of damaging the facial nerve in an experimental procedure.

Lymphatic mapping was performed in 247 lymph node basins (groin 109, axilla 101, neck 21, other sites 16). In 157 patients (79 per cent), biopsy was performed at one site, in 37 patients (19 per cent) at two sites and in five (3 per cent) at three or four sites (mean 1.2 basins per patient). In ten patients, a sentinel node was found outside the groin, neck, axilla or popliteal fossa. The first sentinel node could be identified within 7 min after incision in half of the patients and within 30 min in 95 per cent of patients. The first

sentinel node was found faster in the groin than in all other locations (mean rank 82 for groin *versus* 154 for axilla, 144 for neck and 103 for other sites; $P < 0.001$, Kruskal–Wallis test).

A total of 435 sentinel nodes was excised. In 127 basins (51 per cent) one sentinel node was removed, in 69 basins (28 per cent) two and in 51 basins (21 per cent) three to five (mean 1.8 nodes per basin, 2.2 nodes per patient). Most of the sentinel nodes were both blue and radioactive (86 per cent), 57 nodes (13 per cent) were radioactive only and three nodes (1 per cent) were blue only. No blue vessels or blue nodes were seen in 22 lymphatic basins (9 per cent). Some 86 non-sentinel nodes were excised (mean 0.4 nodes per patient).

Clinical outcome

A sentinel node was tumour positive in 48 patients (24 per cent). The rate of sentinel node involvement for primary tumours 1.0–1.49 mm, 1.5–3.99 mm and 4.0 mm or more thick was 8 per cent (four of 48), 23 per cent (25 of 111) and 53 per cent (19 of 36) respectively (in five patients Breslow thickness could not be assessed reliably and these patients were not included in this analysis). Logistic regression analysis with stepwise backward elimination of non-significant variables was performed to identify factors predicting involvement of a sentinel node (*Table 2*). Six variables were included in the model: Breslow thickness, sex, age, primary tumour location, tumour histology and ulceration. Breslow thickness was the only significant factor. In seven of the 48 patients who underwent therapeutic regional node dissection, additional tumour-positive nodes were found. These seven patients all had a primary melanoma at least 1.6 mm thick.

So far, 15 patients (10 per cent) have had a locoregional or distant recurrence after removal of a negative sentinel node (*Table 3*). Six of these patients relapsed in the previously

mapped basin at 4, 5, 6, 11, 41 and 41 months, without evidence of concomitant locoregional recurrence. These patients may have had a false-negative sentinel node biopsy. Four of these were among the first 41 patients in the study. Occult lymph node metastasis was found in one of the patients with a false-negative biopsy when the sentinel nodes of all patients who had a recurrence were re-examined with additional serial sections and immunohistochemical staining. Eighteen of 48 patients with a tumour-positive sentinel node suffered a relapse. An unexpectedly high incidence of in-transit metastases and satellites was found in this group (six of 48 patients).

Table 3 Site of first recurrence after sentinel node biopsy

Site	Sentinel node status	
	Positive (n=48)	Negative (n=151)
Local	1	3
In-transit/satellite	6	4
Nodal	0	6
Distant	11	2
Total	18 (38)	15 (10)

Values in parentheses are percentages

Table 2 Predictors of a tumour-positive sentinel node

Variable	Parameter estimate	Wald χ^2	P	Hazard ratio
Breslow thickness (mm)	0.46	20.45	<0.001	1.58 (1.30–1.92)
Tumour location				
Leg				1.0
Trunk	0.72	3.11	0.077	2.06 (0.92–4.59)
Head/neck	0.22	0.10	0.76	1.25 (0.30–5.19)
Arm	–0.83	1.49	0.22	0.43 (0.11–1.66)
Age (years)	–0.02	3.23	0.072	0.98 (0.95–1.00)

Values in parentheses are 95 per cent confidence intervals $P > 0.15$ was set as the cut-off for variable elimination

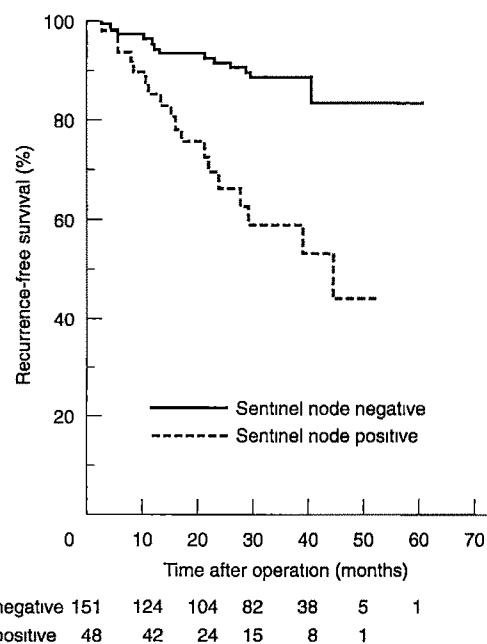


Fig. 1 Kaplan–Meier plot of recurrence-free survival in patients with a tumour-negative or tumour-positive sentinel node. $P < 0.001$ (log rank test)

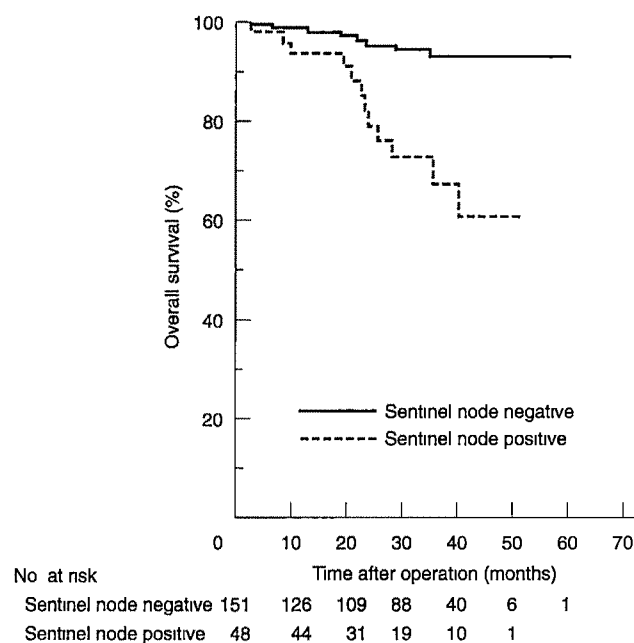


Fig. 2 Kaplan-Meier plot of overall survival in patients with a tumour-negative or tumour-positive sentinel node. $P < 0.001$ (log rank test)

Table 4 Cox multivariate regression analysis for recurrence-free survival: backward elimination method

Variable	Parameter estimate	Wald χ^2	P	Hazard ratio
Involved sentinel node	1.29	11.85	<0.001	3.64 (1.75–7.61)
Breslow thickness (mm)	0.22	9.50	0.002	1.25 (1.08–1.44)
Age (years)	0.05	13.83	<0.001	1.05 (1.02–1.07)
Male sex	0.67	3.18	0.074	1.96 (0.93–4.10)

Values in parentheses are 95 per cent confidence intervals. $P > 0.15$ was set as the cut-off for variable elimination

Table 5 Cox multivariate regression analysis for overall survival: backward elimination method

Variable	Parameter estimate	Wald χ^2	P	Hazard ratio
Involved sentinel node	1.21	5.58	0.018	3.34 (1.23–9.10)
Breslow thickness (mm)	0.23	6.82	0.009	1.26 (1.06–1.50)
Age (years)	0.03	3.53	0.060	1.03 (1.00–1.06)
Male sex	1.07	3.88	0.049	2.92 (1.00–8.49)

Values in parentheses are 95 per cent confidence intervals. $P > 0.15$ was set as the cut-off for variable elimination

The estimated 3-year disease-free survival rate for patients with a tumour-negative or tumour-positive sentinel node was 88 and 58 per cent respectively (Fig. 1). The corresponding overall survival rates were 93 and 67 per cent (Fig. 2). There were eight deaths (from any cause) among patients with a tumour-negative sentinel node, four after a false-negative biopsy and two from causes not related to melanoma. All 12 deaths among patients in the group with a positive sentinel node were from metastatic melanoma.

Cox multiple regression analysis was performed with the following seven variables: Breslow thickness, sentinel node status, sex, age, tumour location, tumour histology and ulceration. Results obtained by the backward elimination method are shown in Tables 4 and 5.

Complications

One patient had a generalized allergic skin reaction to the blue dye. Eighteen patients had a postoperative complication at the lymph node biopsy site: wound infection (six patients), seroma (six), lymphatic fistula (three), haematoma (two), transient neuropraxia of the long thoracic nerve (two) and cutaneous sensory loss (one). Blue discoloration of the skin at the injection site persisted for more than 30 days in 18 patients (9 per cent) and more than a year in six (3 per cent). Ultimately, the blue dye disappeared in all patients.

Discussion

Six (4 per cent) of 151 patients with a negative sentinel node relapsed in the mapped basin. This was the main site of recurrence after removal of a negative sentinel node (six of 15 patients). Long-term follow-up is indeed necessary to establish the reliability of sentinel node biopsy for staging, since two of the possible false-negative biopsies came to light after as long as 41 months. Now, 54 of 200 patients are known to be node positive, of whom six (11 per cent) were discovered during follow-up. Sensitivity was thus estimated to be 89 per cent at most.

The reliability of staging in this series was comparable to the findings of Morton *et al.*¹ and Thompson *et al.*¹⁷ who performed elective lymph node dissection after sentinel node biopsy. Gershenwald *et al.*¹⁵ published similar findings after a longer follow-up. Pijpers *et al.*⁴ found no false-negative biopsies after a mean follow-up of 26 months.

Several explanations are possible for false-negative biopsies. An important finding in the present study was that four of six false-negative operations occurred among the first 41 patients. This may have been due to longer follow-up and to learning phases for surgeons, nuclear medicine physicians and pathologists. Dynamic and lateral scintigraphy images provided useful additional

information. These images have been obtained routinely from the 47th patient onwards. 'Hot' nodes or lymphatic vessels may not be visualized clearly with scintigraphy if they are close to other vessels or nodes, or near the injection site. Sentinel nodes may therefore go unrecognized on the preoperative images. The blue dye technique and the γ probe sufficiently compensated for this shortcoming of scintigraphy. False-negative results may also be due to incomplete pathological examination of the sentinel node. Step-sectioning and immunohistochemical staining are now routine to minimize the risk of missing metastasis in a sentinel node.

False-negative biopsies may also occur because the wrong node has become 'hot' and blue. Intrinsic variability of lymphatic flow or variations in injection technique may decrease the reproducibility of lymphoscintigraphy^{18,19}. The lymphatic flow may also be deviated by a tumour deposit in a lymph node. Lymphatic mapping may be less reliable if the melanoma has previously been excised with wide margins.

Although a false-negative biopsy could worsen the prognosis for an individual patient, the overall clinical impact should be low. The sentinel node biopsy technique may in theory lead to improved prognosis in about seven of 100 patients. An estimated 80 patients who do not have lymph node metastases and about nine with both nodal and distant disease at the time of diagnosis will not benefit from early lymph node dissection. Approximately four of the remaining 11 patients with lymph node metastases only at the time of diagnosis can also be cured if dissection is performed at a later stage²⁰. The number of patients who can possibly benefit from sentinel node biopsy will be further decreased from seven to six because of the potential for a false-negative result.

This study confirms the findings of Gershenwald *et al.*¹⁶ that sentinel node status is an important prognostic factor, even with a false-negative rate of at least 11 per cent. The randomised Multicentre Selective Lymphadenectomy Trial, initiated by D. L. Morton at the John Wayne Cancer Institute in Santa Monica, California, USA, will reveal the impact of sentinel node biopsy on survival, morbidity and quality of life. The procedure remains experimental until a survival benefit is proven or effective adjuvant therapy becomes available.

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Vascular Surgical Society of Great Britain and Ireland

The following abstracts are from the papers presented at the 33rd Annual Conference of the Vascular Surgical Society of Great Britain and Ireland,

held in Leicester, UK, on 24–26 November 1999. President of the Society, Professor P. R. F. Bell, was in the Chair.

Infrainguinal bypass grafting for critical ischaemia in the hands of trainees

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Background: Changes in surgical training mean that operative experience must be gained more efficiently. However, it is important to demonstrate that increasing training opportunities are not associated with inferior patient outcome. The immediate and long-term outcomes of patients undergoing infrainguinal bypass surgery by consultants and trainees were compared.

Methods: A prospectively gathered database of 1077 infrainguinal bypasses performed on 1003 patients for chronic critical limb ischaemia between 1 January 1983 and 31 December 1998 in a single regional vascular unit was evaluated.

Results: Consultants performed 733 operations (68.1 per cent), 347 (47.3 per cent) above-knee, 257 (35.1 per cent) below-knee popliteal, 121 (16.5 per cent) crural and eight (1.1 per cent) other procedures. Of 344 trainee operations, 170 (49.4 per cent) were above-knee, 122 (35.5 per cent) below-knee, 48 (14.0 per cent) crural and four (1.2 per cent) other operations. There was no significant difference in 30-day mortality rate between consultant (2.8 per cent) and trainee (2.0 per cent) operations, nor was there any significant difference in patency or limb salvage rates at 36 months (*Table*). There was a trend towards reduced graft patency in trainee crural bypasses but this was not statistically significant (35.9 *versus* 56.2 per cent; $P = 0.14$, log rank test).

	Synthetic	Synthetic + vein cuff	Vein
Consultant			
3-year patency (%)	50.0 ($n=234$)	54 ($n=83$)	64.9 ($n=416$)
Limb salvage (%)	68.2 ($n=234$)	73 ($n=83$)	78.3 ($n=416$)
Trainee			
3-year patency (%)	59.1 ($n=105$)	42 ($n=55$)	67.7 ($n=184$)
Limb salvage (%)	77.8 ($n=105$)	59 ($n=55$)	82.7 ($n=184$)

Conclusion: These data suggest that, with appropriate case selection and supervision, training in femoropopliteal and crural bypass grafting does not compromise early or long-term outcome.

Lower extremity arterial injury: results of 550 cases and review of risk factors associated with limb loss

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Background: The authors' experience of lower limb arterial injury (LLAI) management was analysed and risk factors associated with limb loss were identified.

Methods: Between 1987 and 1997, data on 550 patients with 646 LLAI were analysed retrospectively.

Results: The mechanism of LLAI was gunshot wounds in 46 per cent, blunt trauma in 19 per cent, stabbing in 12 per cent and shotgun in 9 per cent. The most frequently injured vessel was the superficial femoral artery (37 per cent) followed by the popliteal (31 per cent), crural (11 per cent), common femoral (9 per cent) and profunda (59 per cent) arteries. In 3 per cent of patients there was a combined injury on either side of the knee. Associated injuries included bony injury in 35 per cent, nerve injury in 8 per cent and remote injuries affecting the head, chest or abdomen in 4 per cent. Surgery was carried out in 96 per cent of patients with a limb salvage rate of 84 per cent and a survival rate of 98 per cent. Despite a rising trend in LLAI, total and delayed amputation rates remained stable. On stepwise logistic regression analysis, significant ($P < 0.01$) independent risk factors for amputation were blocked graft (odds ratio (OR) 16.7), combined above- and below-knee injury (OR 4.4), tense compartment at presentation (OR 4.2), arterial transection (OR 2.8) and associated compound fractures (OR 2.7). Factors such as simple fractures, venous injury/ligation and the use of synthetic grafts were not associated with increased risk of limb loss.

Conclusion: LLAI carries a high amputation rate. Stab injuries are the least likely to lead to amputation whereas injuries associated with severe soft tissue damage, such as high-velocity firearm injuries and blunt trauma with compound fractures, are the most likely to do so. The most significant independent risk factor for limb loss was failed revascularization.

Exercise in claudicants is associated with systemic fibrinolysis

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Background: Claudicants have been shown to mount a potentially harmful systemic inflammatory response to exercise, characterized by vascular endothelial activation and thrombin generation. However, the fibrinolytic response to exercise remains unknown. This study aimed to determine the nature of the fibrinolytic response to exercise in claudicants and normal controls.

Methods: Peripheral venous blood was drawn from 18 claudicants and eight age- and sex-matched controls before, immediately and 1, 5, 10, 20, 40 and 60 min after treadmill exercise (Gardner protocol). Claudicants exercised to the point of maximal ischaemic pain and controls to the point of fatigue. Plasma tissue plasminogen activator (tPA) activity and plasminogen activator inhibitor (PAI) 1 activity were measured by 'Coaset' PAI and 'Coatest' tPA assays (Chromogenix, Sweden).

Results: There was no significant difference in tPA or PAI-1 activity between the groups at baseline. tPA activity increased significantly immediately after exercise in all claudicants (median (interquartile range) 2.8 (1.6–4.0) *versus* 5.6 (3.5–7.7) units ml⁻¹; $P=0.003$, Wilcoxon test) and remained significantly raised for 10 min. This was accompanied by an immediate significant fall in PAI-1 activity (8.5 (4.3–12.7) *versus* 8.3 (5.0–11.6) units ml⁻¹; $P=0.04$) which normalized by 10 min. Neither tPA activity or PAI-1 levels changed significantly in the control group.

Conclusion: These data indicate that exercise in claudicants is associated with systemic fibrinolysis. The immediacy and short-lived nature of the response suggests that it occurs as a consequence of muscle ischaemia rather than reperfusion.

Prevalence and treatment of hypercholesterolaemia in patients with peripheral vascular disease

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Background: Hypercholesterolaemia is a recognized risk factor for the development of arteriosclerosis. There is compelling evidence to support the use of lipid-lowering strategies in all hypercholesterolaemic patients with arteriosclerotic disease. In peripheral arterial disease (PAD), national guidelines recommend treatment if total cholesterol exceeds 5.0 mmol l⁻¹. The prevalence of hypercholesterolaemia in patients with PAD was determined and the adequacy of lipid management before vascular referral was examined.

Methods: This was a prospective study of 233 consecutive patients admitted electively to this vascular surgery unit between December 1997 and December 1998. Some 68 patients were admitted with carotid disease, 81 with an aneurysm and 84 with intermittent claudication. A fasting venous blood sample was obtained from each patient.

Results: There were 175 men and 58 women, of median age 67 (range 37–85) and 68 (range 47–85) years respectively. Only 35 patients (15 per cent) were previously known to be hypercholesterolaemic; all but one were receiving treatment (one dietary, 33 statin). Of the remaining 198 patients, 124 (63 per cent) had a serum cholesterol level above 5.0 mmol l⁻¹. A further 17 patients (9 per cent) had total cholesterol/high-density lipoprotein cholesterol ratio greater than 5.0; these patients may also benefit from lipid-lowering therapy. In total, 141 (80 per cent) of 176 hypercholesterolaemic patients were undiagnosed at the time of hospital admission.

Conclusion: Hypercholesterolaemia is an important and correctable risk factor found in the majority of patients with PAD, but despite national guidelines and clear evidence from randomized controlled trials it is simply not being diagnosed in primary care. All elective patients with PAD should be screened for hypercholesterolaemia during their admission.

Prosthetic femoropopliteal bypass: randomized comparison of polytetrafluoroethylene and heparin-bonded Dacron

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Background: Dacron was largely abandoned for femoropopliteal bypass 30 years ago as saphenous vein achieved better patencies. As patency in prosthetic above-knee (AK) femoropopliteal bypass in patients on aspirin is equivalent to that with saphenous vein, heparin-bonded Dacron (HBD) and polytetrafluoroethylene (PTFE) have been compared in a randomized trial involving ten hospitals which also included below-knee (BK) popliteal or tibioperoneal trunk bypass where the long saphenous vein was absent or inadequate.

Methods: Over a 28-month recruitment period, 209 patients undergoing femoropopliteal bypass (180 AK, 29 BK) were randomized by the method of minimization to HBD ($n=106$) or PTFE ($n=103$). Aspirin 300 mg day⁻¹ was started before surgery and continued unless the patient was intolerant.

Results: Mean follow-up was 34 (range 19–48) months. Fifteen patients (7 per cent) died with patent grafts and three (1 per cent) infected grafts were removed. Patency (measured by Kaplan–Meier survival analysis) was 70, 63 and 55 per cent at 1, 2 and 3 years for HBD, compared with 56, 46 and 42 per cent respectively for PTFE ($P=0.0444$). Patency at 3 years for AK bypass was significantly better than that for BK bypass. A total of 70 interventions were performed on 47 patients, achieving long-term patency in only three. Amputations were performed in 23 patients, six with HBD and 17 with PTFE grafts ($P=0.015$, Fisher's exact test).

Conclusion: In femoropopliteal bypass, primary patency was better with HBD than PTFE, and HBD was associated with a lower amputation rate.

Staged *in situ* bypass

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Background: After femoral revascularization, following embolectomy or proximal reconstruction, the need for additional distal revascularization may be unpredictable. This dilemma may be addressed by anastomosing the detached upper end of the long saphenous vein to the femoral arteriotomy, as for *in situ* bypass, permitting some outflow into proximal vein tributaries. Later, if ischaemia persists, distal arterial flow can be established by closed retrograde saphenous valvulotomy.

Methods: Over 12 years this technique was employed in 26 legs in 22 patients, following inflow reconstruction in 15 and femoral embolectomy in seven. Postoperative observation showed persisting distal ischaemia in 14 legs and distal bypass was completed after 1–9 days, using local anaesthesia without femoral re-exposure. One patient died at 15 days and 13 grafts were patent on discharge from hospital.

Results: In 12 legs in 11 patients, limb perfusion was deemed adequate after operation. Four patients (five legs) died in hospital and seven were discharged. No further procedure was required in five and the proximal long saphenous vein presumably thrombosed. In two legs the whole long saphenous system had become pulsatile at 7 and 8 months, and a distal bypass was completed. No amputations were required in this series.

Conclusion: Staged *in situ* bypass can avoid prolonged and complex reconstructions in frail patients and facilitates the use of local anaesthesia, where necessary.

Endoluminal repair of abdominal aortic aneurysm causes more perioperative renal dysfunction than open repair

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Background: In this prospective case-control study the aim was to compare perioperative renal function in well matched patients undergoing open repair (OR) (group 1) or endoluminal repair (ER) (group 2) of an abdominal aortic aneurysm (AAA) and preoperative renal function in other patients undergoing ER (group 3) with function 1–3 years after surgery.

Methods: Of 73 patients undergoing AAA repair, 45 were recruited to the study as follows: 14 patients (median age 77 years, 12 men) to group 1, 14 patients (median age 76 years, 11 men) to group 2 and 17 patients (median age 76 years, 14 men) to group 3. Serum creatinine, creatinine clearance and/or glomerular filtration rate (GFR) were measured coupled with ^{99m}Tc -radiolabelled mercaptoacetyl triglycine (MAG3) renal studies. From the MAG3 renal scans, perfusion, split renal function, mean parenchymal transit time (MPTTI) and outflow pattern were assessed. Groups 1 and 2 underwent scintigraphic evaluation before, and 8 days after operation. Group 3 was assessed before operation and 1–3 years later.

Results: Fifteen of 31 patients undergoing ER had preoperative renal dysfunction (GFR less than 50 ml min^{-1}) compared with two of 14 who had OR. Ten patients from groups 2 and 3 developed severe renal dysfunction. Of these, two died, one required haemodialysis (graft deployed over the renals), two were dialysis-free but developed worsening renal function and five regained their previous renal function. In four patients who had ER, differential function improved, in one with retroperitoneal fibrosis it deteriorated and in nine it was unchanged. See Table below.

Conclusion: ER is associated with a greater degree of perioperative renal dysfunction than OR. In the absence of technical problems with endograft deployment, renal function in ER in the long term is not adversely affected.

Thoracic aortic stent grafts

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Background: Open surgical intervention for aneurysms of the distal arch and descending thoracic aorta is associated with high morbidity and mortality rates. Stent grafts offer an attractive alternative treatment for these aneurysms.

Methods: Thirteen patients were treated from July 1997 to August 1999. Eight patients had atheromatous aneurysms; five were elective and three urgent for dysphagia, stridor and back pain. The mean age of these patients was 77 (range 64–90) years. Another five urgent cases comprised transection (two), traumatic dissection (one), acute dissection (one) and secondary aorto-oesophageal fistula (one). The mean age of these patients was 43 (range 18–77) years. The types of stent

	Group 1			Group 2			Group 3		
	Preop	Postop	P	Preop.	Postop	P	Preop	Postop	P
Serum creatinine ($\mu\text{mol l}^{-1}$)	122 (82–210)	161 (90–260)	<0.008	130 (81–200)	181 (80–341)	<0.01	124 (68–256)	146 (68–491)	n.s.
GFR (ml min^{-1})	52 (30–110)	47 (23–108)	<0.01	51 (29–84)	39 (8–97)†	<0.008	49 (20–90)	43 (0–114)	n.s.
MPTTI (s)*	190	270	<0.02	172	267‡	<0.002	195	210	n.s.

Values are median (range). *Normal <240 s. n.s., Not significant. †P<0.003, ‡P<0.01 versus group 1 postop

graft used were Excluder (six), AneuRx (five), Vanguard (one) and Stenford (one). Additional surgical procedures included carotid-to-carotid bypass, exposure of the common iliac artery (as the device was too short to reach the proximal descending thoracic aorta) and repair of a symptomatic infrarenal aortic aneurysm.

Results: One patient with acute aortic dissection 1 month after myocardial infarction died from pulmonary embolus and myocardial reinfarction (mortality rate 8 per cent). One patient who suffered a stroke with good recovery was discharged on day 21 but died from pneumonia at 8 weeks. All aneurysms were excluded on computed tomography apart from the traumatic dissection in which perfusion of the false lumen continued retrogradely. No patient suffered paraplegia or renal failure. No ward patient required admission to the intensive care unit.

Conclusion: Thoracic stent grafts offer a realistic alternative to open surgery, but long-term follow-up is required to assess durability.

RETA: update on the short-term (30 day) and long-term (1 and 2 years) results of endovascular repair of abdominal aortic aneurysms

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Background: The updated results from the Registry of Endovascular Treatment of Aneurysms (RETA) for short- and long-term outcomes from 3 years of data collection are presented.

Methods: Some 611 patients were submitted to RETA from January 1996 to December 1999 from 31 centres. In the same period 1-year follow-up was received for 299 of the 340 cases requested (88 per cent return rate) and 2-year follow-up for 88 of the 155 cases requested (57 per cent return rate).

Results: At 30 days 90 per cent of abdominal aortic aneurysms (AAA) were excluded. The rate of conversion to open repair was 5 per cent. Complications occurred in 25 per cent of patients. The overall 30-day mortality rate was 7 per cent with significantly more deaths in the aortouni-iliac and crossover groups (12 *versus* 4 per cent; adjusted odds ratio (OR) 2.6 (95 per cent confidence interval (c.i.) 1.2–5.9; $P=0.018$), in unfit patients (18 *versus* 4 per cent, adjusted OR 4.3 (95 per cent c.i. 2.0–9.5); $P<0.001$) and in patients with larger aneurysms (10 *versus* 2 per cent; adjusted OR 4.4 (95 per cent c.i. 1.4–13); $P=0.009$). At 1 year the mortality rate was 11 per cent, with four deaths (1 per cent) due to ruptured AAA. New complications were reported in 53 patients (20 per cent) with 31 (12 per cent) related to the device or AAA. In the second year of follow-up the mortality rate was 11 per cent with one death (1 per cent) due to ruptured AAA. New complications in the second year after device placement were reported in 24 per cent of patients, with 16 (20 per cent) related to the device or AAA. The

cumulative endoleak-free survival for all patients was 57 per cent at 2 years.

Conclusion: The 30-day mortality rate for endovascular repair was comparable to reported results for conventional surgery, particularly in fit patients. There was a relatively high complication rate at follow-up, with ruptures reported. Most complications had endovascular treatment.

Differences in cognitive function and S100 production after carotid endarterectomy under local or general anaesthetic

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Background: Previous studies reported both improved (enhanced cerebral perfusion after carotid endarterectomy (CEA)) and diminished (intraoperative ischaemic injury) cognitive function (CF) following CEA. These studies were not adequately controlled for anxiety, general health and learning (repeated testing), and the influence of anaesthetic technique was not assessed.

Methods: This study assessed CF (trained psychologist, seven computerized tests) before operation, and at 5 and 90 days after CEA performed under local anaesthesia (LA) ($n=34$) or general anaesthesia (GA) ($n=13$). Similar measurements in patients undergoing lower limb revascularization ($n=14$) and unoperated subjects with asymptomatic carotid stenosis greater than 70 per cent ($n=16$) tested twice, 3 months apart, controlled for the effects of anaesthesia, surgery and carotid arteriosclerosis. Additionally, jugular venous S100 levels (neuronal protein released following cerebral injury) were measured (before carotid clamping, and 1, 4 and 24 h after clamp release) in 18 of these patients (nine LA, nine GA).

Results: Compared with controls, test performance in patients who had CEA under GA improved in one (executive CF 90 days; $P=0.028$), but deteriorated in another (working memory 90 days; $P=0.038$) while patients who had LA improved in three of seven tests (executive function, working memory) at 5 days ($P=0.03$, 0.048, 0.036) and 90 days ($P=0.01$, 0.05, 0.006). Further, a greater than 25 per cent improvement in one or more tests was more likely 90 days after CEA under LA (22 of 34 *versus* four of 13; $P<0.04$) with improved executive function, speed and accuracy. S100 levels were lower after CEA under LA (1 h: 0 (0–30) *versus* 29 (8–98) $\mu\text{g ml}^{-1}$, $P<0.05$; 4 h: 0 (0–6) *versus* 22 (2–95) $\mu\text{g ml}^{-1}$, $P<0.05$; 24 h: 0 (0–1) *versus* 35 (14–77) $\mu\text{g ml}^{-1}$, $P<0.01$).

Conclusion: This study demonstrated improved CF following CEA under LA which was associated with lower jugular venous S100 levels (marker of cerebral injury). These differences may reflect improved cerebral oxygenation (preservation of cerebral autoregulation).

Role of the neutrophil in the development of sepsis following abdominal aortic aneurysm surgery

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Background: There is evidence to suggest that the neutrophil (PMN) plays a critical early step in development of the ischaemia-reperfusion syndrome and sepsis. Not all patients undergoing aortic aneurysm repair develop these postoperative complications. The PMN receptor CD16 plays an important role in phagocytosis, cell-mediated cytotoxicity and the release of free radicals and proteolytic enzymes. This study determined if there is any relationship between PMN CD16 expression, phagocytosis and the development of sepsis.

Methods: Some 50 patients (39 men and 11 women, median age 70 years) who underwent elective infrarenal abdominal aortic aneurysm repair were studied. Venous blood was taken before operation, throughout surgery and for 7 days afterwards. CD16 was measured, unstimulated and following further stimulation with phorbol myristate, lipopolysaccharide and *N*-formyl-methionyl-leucyl-phenylalanine using flow cytometry. Phagocytosis was measured using flow cytometry and the production of elastase using an enzyme-linked immunosorbent assay. Sepsis was defined according to the ACCP/SCCM definition.

Results: There were 36 uncomplicated operations and 14 patients with sepsis. There was no difference between the two groups in respect of nutritional, co-morbid or technical factors. In the group that developed septic complications, the level of PMN CD16 expression was significantly higher before operation (30.2 *versus* 10.4 mcf; $P < 0.05$, Mann-Whitney *U* test) and throughout the postoperative period. Surgery produced no change in CD16 expression in either the septic or uncomplicated group. Stimulation of the PMNs before operation caused an increase in CD16 expression in both groups. After operation, stimulation of PMNs in the septic group resulted in a fall in CD16 expression (40.8 *versus* 20.4 mcf, $P < 0.05$, Mann-Whitney *U* test); surgery produced no change in the level of expression in the uncomplicated group. Phagocytic ability was comparable before operation (91.2 *versus* 94.2 mcf), but showed a greater reduction in the septic group after operation (73.4 *versus* 86.2 mcf; $P < 0.05$, Mann-Whitney *U* test). Elastase concentration was also similar before operation (48 *versus* 49 $\mu\text{g l}^{-1}$); after operation, there was a greater increase in the septic group (166 *versus* 104 $\mu\text{g l}^{-1}$; $P < 0.05$, Mann-Whitney *U* test).

Conclusion: This study provides evidence of functional differences in PMN behaviour in patients who subsequently develop sepsis following aneurysm surgery. This difference occurs early in the postoperative course and it may be possible to identify these patients before operation.

Effect of stockings on calf muscle oxygenation in patients with venous insufficiency

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Background: The mechanism of action of stockings in symptom relief and treatment of venous insufficiency is still inadequately understood. Near-infrared spectroscopy (NIRS) provides continuous non-invasive monitoring of changes in tissue oxygen reserves and availability, by monitoring oxyhaemoglobin (HbO₂), deoxyhaemoglobin (HbD) and cytochrome oxidase (CtO₂). This study investigated the effect of stockings on calf muscle oxygenation during exercise using NIRS in patients with venous insufficiency.

Methods: Ten patients (mean (s.e.m.) age 56(5) years, seven women) with venous insufficiency participated in the study. Patients rested in a supine posture for 20 min. NIRS probes were attached to the calf at interoptodes spacing of 4 cm and initialized to zero. Calf oxygenation was continuously monitored during standing followed by a 5-min slow walk at 1.6 km h⁻¹ with and without stockings chosen at random. A 30-min rest in the supine position was allowed between stockings. Pulse rate and peripheral oxygen saturation were monitored continuously by a pulse oximeter.

Results:

	No stocking	Class 1	Class 2	Class 3
Mean HbO ₂ (μmol l ⁻¹)	2.88(2.39)	4.29(2.41)	4.52(2.43)	5.83(2.44)‡
Mean HbD (μmol l ⁻¹)	-8.53(2.10)	-4.20(2.38)*	-3.19(3.21)†	-1.06(3.34)*
Mean CtO ₂ (μmol l ⁻¹)	0.73(0.65)	0.93(0.60)	1.36(0.65)*	1.71(0.72)*

Values are mean (s.e.m.). HbD, oxygenation index * $P \leq 0.002$, † $P = 0.01$, ‡ $P = 0.03$ *versus* no stocking (paired *t* test)

Mean HbO₂ concentration, HbD and mitochondrial oxygenation (CtO₂) increased significantly with stockings during exercise.

Conclusion: Graduated compression stockings may achieve beneficial effects by improving calf muscle oxygenation during exercise in patients with venous insufficiency.

Intraoperative change in baroreceptor function during carotid endarterectomy

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Background: Labile blood pressure following carotid endarterectomy (CEA) is common and is associated with perioperative myocardial infarction and intracranial haemorrhage. Previous studies have identified that alteration in carotid baroreceptor function is responsible for the blood pressure changes although the mechanism remains unclear. This study aimed to identify the mechanism by which CEA affects baroreceptor function.

Methods: Fifty patients were recruited prospectively and underwent estimation of baroreceptor sensitivity (BRS) during

a 10-min period of supine bed rest using electrocardiography and Finapres, 2 days before and 2 days to 6 weeks after surgery. During surgery continuous measurements of blood pressure (intra-arterial) and heart rate were recorded on to digital audio tape for postoperative analysis. During analysis the operation was divided into different stages to identify at which stage baroreceptor function altered. Particular attention was paid to initial clamping of the carotid artery, performance of the endarterectomy and final restoration of blood flow. In addition the carotid sinus area was stimulated by stroking the inside of the artery before and after removal of the plaque. Autonomic activity was calculated using power spectral analysis of beat-to-beat blood pressure and the R-R interval from the electrocardiograph. BRS was estimated by calculation of the square root of the ratio of the powers of R-R interval and systolic blood pressure to give the alpha index which has been shown to correlate well with BRS calculated by means of standard pharmacological techniques.

Results: For this cohort of patients BRS was significantly reduced 2 days after surgery compared with the preoperative recordings (2.8(0.4) to 5.6(0.8)). Six weeks after operation BRS had improved but had not achieved preoperative levels (3.8(0.6) to 5.6(0.8)). During surgery, patients with good baroreceptor function identified before operation experienced a rise in blood pressure on initial carotid clamping indicating that dissection had not affected the baroreceptor mechanism. Similarly, intraluminal stimulation of the carotid sinus area with the plaque *in situ* produced a decrease in blood pressure indicating good baroreceptor function. After removal of the plaque, repeating the intraluminal stimulation did not produce a decrease in blood pressure indicating disruption of the baroreceptor mechanism.

Conclusion: Removal of the atheromatous plaque during CEA adversely affects carotid baroreceptor function. The baroreceptor mechanism is disrupted but not completely destroyed and gradually improves in the weeks following surgery.

Prospective comparison of recurrent venous ulceration after superficial surgery or compression bandaging

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Background: The purpose of this prospective study was to investigate and compare the recurrence rate of venous ulcers treated by superficial surgery or compression bandaging.

Methods: Patients received treatment for ulcers between May 1994 and July 1997. All legs in the study had an ankle : brachial pressure index above 0.8. The superficial surgery group consisted of 91 legs with superficial venous incompetence and normal deep veins which healed after superficial surgery. This group did not receive postoperative compression bandaging or hosiery. The community compression bandaging group consisted of 152 legs that healed during the recruitment period. A recurrent ulcer was defined as a further episode of venous ulceration in a previously healed leg. Patient follow-up

was by surgeons, district nurses' telephone call and/or letter. Recurrence rates were calculated by life-table analysis (Kaplan-Meier). Patients who died or were lost to follow-up were censored to their last visit.

Results: The recurrence rate in the superficial surgery group at 1 and 2 years was 3 and 6 per cent respectively, compared with 26 and 33 per cent respectively in the compression bandaging group. The differences between the superficial surgery and compression bandaging groups were statistically significant ($P = 0.00001$, log rank test).

Conclusion: Ulcer healing after superficial surgery is sustained in the absence of postoperative compression. Conversely, the ulcer recurrence rate after compression bandaging is very high, probably because the underlying venous abnormality has not been corrected. The follow-up of this study needs to be continued to 5 years, but the data so far suggest that a prospective randomized study comparing superficial surgery with compression bandaging is required.

Carotid artery plaque morphology is related to time since last neurological event

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Background: Conflicting conclusions have been drawn regarding the relationship of plaque morphology and symptomatology of carotid atherosclerosis. Previous papers have examined the nature of symptoms and the degree of stenosis. This study determined whether plaque morphology was related to symptomatology with regard to the nature, timing and amount of symptoms, and the degree of stenosis.

Methods: In 60 consecutive carotid endarterectomies the symptoms (transient ischaemic attack (TIA), cerebrovascular accident (CVA), amaurosis fugax (AF), other), time between last neurological event and surgery, number of episodes and the degree of stenosis were recorded prospectively. The plaques removed at surgery were examined immediately and by histology. The macroscopic appearance was recorded as stable (fibrous or fatty plaque with or without calcification) or unstable (plaques with ulceration, rupture or thrombosis). Microscopic grading as either stable or unstable was done using the criteria of a consensus document (*Circulation* 1995).

Results: There were more CVAs (11 of 34 *versus* four of 26), and fewer TIAs (17 of 34 *versus* 16 of 26) and instances of AF (six of 34 *versus* six of 26) when the plaque was deemed unstable, but this was not statistically significant. Twenty of 34 patients with an unstable plaque had an event in the 6 weeks preceding surgery compared with one of 26 with a stable plaque ($P < 0.001$). Unstable plaques were associated with more events (12 of 34 patients had more than three events compared with one of 26 with a stable plaque; $P = 0.012$). Degree of stenosis was not related to plaque morphology. In a logistic regression model, the only predictive factor for finding an unstable plaque at surgery was the timing of the last neurological event ($P < 0.001$).

Conclusion: The importance of time since the last neurological event in predicting plaque instability is shown. This factor may help to clarify future studies attempting to determine plaque morphology before operation by ultrasonography.

Ruptured abdominal aortic aneurysm: difference in selection criteria for surgery between vascular surgeons in district general and teaching hospitals

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Background: This audit was devised in order to examine outcome following presentation with ruptured abdominal aortic aneurysm (AAA) in one Deanery. Identification of differences in practice and outcome were sought.

Methods: Some 18 consultant vascular surgeons in eight district general hospitals (DGHs) and one university hospital (UH) participated in a prospective audit of ruptured AAA from March 1997 to February 1998.

Results: Some 159 patients were included in the audit. Outcome is shown in the *Table* below.

	UH		DGH
	A and E admissions	Transferred admissions	Overall
Total admissions	22	25	112
Surgical repair	20	23	63
Alive	8	11	30
Dead	12	12	30
30-day mortality (%)	60	52	56
No surgery group	2	2	49
Overall mortality (%)			59
Missing data			3

A and E, accident and emergency

There was no difference in operative mortality rate between the UH and DGHs nor was there an increased mortality rate in the group of patients transferred from hospital to hospital despite

the time delay incurred. In 47 patients admitted to the UH serum creatinine was the only laboratory test which correlated with outcome.

Conclusion: This audit clearly highlighted the differing attitude to selection of patients for surgery between the vascular surgeons in the UH and DGHs, although there was no overall statistical difference in outcome.

Mortality rate of elective abdominal aortic aneurysm repair is lower in screened men

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Background: It is expected that the main benefit of abdominal aortic aneurysm (AAA) screening will be derived from differences in the mortality rate between elective and ruptured AAA repair. There may also be differences in elective AAA mortality rate between screened and non-screened patients, and the aim of this study was to compare mortality rates for these two groups using standard statistical analysis, Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) and P-POSSUM scoring.

Methods: Patients undergoing elective AAA repair were either from a current screening programme to detect men over 65 years with AAA (screened) or were referred from other sources (non-screened). All patients were scored using the POSSUM scoring system. Mortality data were studied. Agreement between observed and expected deaths for POSSUM and P-POSSUM for screened and non-screened patients was determined.

Results: Some 276 elective AAA repairs were performed with an overall mortality rate of 6.9 per cent (see *Table* below). The mortality rate of 2.7 per cent for 111 screened patients was significantly less than that of 9.7 per cent for 165 non-screened patients (Pearson $\chi^2 = 5.06$, $P = 0.02$). Actual *versus* predicted death ratio for all elective patients was 0.93 for POSSUM and 2.38 for P-POSSUM.

Conclusion: Screened patients have a lower mortality rate than non-screened patients for AAA repair. POSSUM scoring

Risk of death (%)	Screened patients				Non-screened patients			
	No. of operations	Mean risk (%)	Predicted deaths	Reported deaths	No. of operations	Mean risk (%)	Predicted deaths	Reported deaths
POSSUM								
0-4	31	3.21	1	1	36	3.09	1	4
4-10	73	5.99	4	1	91	6.48	6	7
10-25	7	14.42	1	1	33	15.22	5	4
25-60	0				5	38.48	2	1
P-POSSUM								
0-4	104	1.50	2	2	128	1.71	2	11
4-10	7	6.70	0	1	27	6.59	2	3
10-25	0				7	15.24	1	1
25-60	0				3	41.45	1	1

provides the best prediction of death in this elective AAA group.

Indications of infection with *Chlamydia pneumoniae* are associated with expansion of abdominal aortic aneurysm

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Background: This was a study of the possible association between the progression of abdominal aortic aneurysm (AAA) and indicators of infection with *Chlamydia pneumoniae*.

Methods: Blood samples were taken from patients with AAA (3 cm diameter or greater detected by an aneurysm screening programme) who had been followed prospectively for up to 11.5 (mean 4.1) years. A sex- and age-matched control group was also recruited. Immunoglobulin (Ig) G and IgA antibodies against *C. pneumoniae* were measured by a microimmunofixation test. Analysis of variance, multiple linear regression and logistic regression were used for statistical analysis. Ninety men and ten women with a small AAA and 20 age-matched male controls were investigated. Outcome measures studied were AAA expansion, and IgA and IgG titres of antibodies against *C. pneumoniae*.

Results: Forty-four (95 per cent confidence interval (c.i.) 31–55) per cent of the men with an AAA had IgA greater than 64 or IgA above 28 compared with 10 per cent of the women with an AAA (odds ratio (OR) 7.2 (95 per cent c.i. 1.0–160.8)) and 25 per cent of the controls (OR 2.24 (95 per cent c.i. 0.67–7.93)). IgA greater than 128 was significantly associated with greater expansion (5.3 versus 2.6 mm per year), even after adjustment for initial AAA size and age. A significant dose–response reaction was found between IgA titre and mean annual expansion ($R=0.45$ (95 per cent c.i. 0.24–0.62)). The significant positive correlation remained after adjusting for initial AAA size and age. Finally, IgG greater than 128 was present significantly more often in patients with expansion above 1 cm annually (OR 12.6 (95 per cent c.i. 1.4–293)).

Conclusion: A high proportion of men with AAA have signs of infection by *C. pneumoniae*. The progression of AAAs correlated with the presence of indicators of *C. pneumoniae* infection, and a dose–response reaction between IgA titre and expansion was observed.

Population screening reduces the total community mortality rate from aortic aneurysms

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Background: Screening of the male population for unsuspected abdominal aortic aneurysm (AAA) has been taking place in a single UK county (population 520 000) since 1990.

Methods: The general practitioner surgery-based programme involves ultrasonographic examination of each year's new batch of 65-year-old men, excluding those who were older than this when the programme started. This method of screening has resulted in a gradually enlarging cohort of screened men, so that by the end of 1998 all men between the ages of 65 and 73 years had been offered an ultrasound scan, with 85 per cent accepting and over 21 000 men examined. Total aneurysm-related deaths in the community have been quantified by examining inpatient records and post-mortem results for the county's hospitals, together with computerized death certificate records held by the health authority (available for 1994 onwards). This figure thus includes deaths at home from ruptured AAA, in-hospital deaths from ruptured AAA with or without emergency surgery and all deaths following elective AAA surgery.

Results: The 65–73-year-old age group has been progressively influenced by AAA screening as new 65 year olds are examined each year. Total aneurysm-related deaths in this age range have shown a progressive, year by year fall between 1994 and 1998, with an overall reduction in deaths by two-thirds during this 5-year period. In contrast, aneurysm-related deaths in men aged below 65 and over 73 years have tended to show a slight increase in the same period.

Conclusion: These figures clearly demonstrate that population screening reduces overall deaths from aortic aneurysms.

Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm

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Background: In regional and national studies death within 30 days of elective open surgical repair of an abdominal aortic aneurysm has been reported to be 7–8 per cent or even higher. Identification of preoperative factors associated with this mortality risk is important for informing surgical policy and may suggest suitable preoperative interventions.

Methods: During the course of the UK Small Aneurysm trial, 820 patients aged 60–80 years underwent elective open surgical repair of an abdominal aortic aneurysm. The relationship between 30-day mortality rate and 13 prespecified potential prognostic factors (including age, sex, aneurysm diameter, electrocardiographic evidence of myocardial ischaemia, lung function, creatinine level, hospital centre and tube or bifurcated graft) was studied.

Results: The postoperative mortality rate was 5.6 per cent overall (46 deaths in 820 patients). In univariate analyses postoperative mortality risk was associated significantly with higher serum creatinine ($P=0.002$), poor lung function with low forced expiratory volume in 1 s (FEV_1) ($P=0.003$) and older age ($P=0.03$). Evidence of the relationship between age and postoperative death was weaker ($P=0.08$) after adjustment for creatinine and FEV_1 . The predicted postoperative mortal-

ity risk ranged from 2.7 per cent in younger patients with a low creatinine level and high FEV₁ to 7.8 per cent in older patients with above average creatinine levels and below average FEV₁. There was no evidence of between-hospital or between-surgeon variability in postoperative risk.

Conclusion: Poor preoperative lung and renal function were associated strongly with postoperative death. Age was less important once these two prognostic indicators were taken into account. The potential for preoperative improvement in lung and renal function to reduce the postoperative mortality rate should be addressed in future studies.

Prospective randomized multicentre double-blind placebo-controlled trial of the use of aprotinin in ruptured abdominal aortic aneurysm repair

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Background: This study assessed whether the use of aprotinin affects the number of blood products transfused, and the morbidity and mortality rates associated with the repair of a ruptured abdominal aortic aneurysm (AAA).

Methods: Nine centres with local ethics committee approval for the trial were involved in the recruitment of 77 patients. A bolus of either 2 million units of aprotinin, followed by an infusion of 500 000 units every 30 min, or placebo, was prepared and aprotinin was administered to 38 patients, with 39 receiving the placebo. The number of blood products transfused during surgery and in the first 12 h after operation was noted, along with the incidence of complications, mortality rates and length of hospital stay. Analysis of the difference between blood product transfusion was by the Kruskal–Wallis test.

Results: Seventeen of the 38 patients receiving aprotinin and 17 of the 39 given placebo died within 30 days, with an overall mortality rate of 44 per cent. The median amount of blood given to the aprotinin group after operation was 1 (range 0–14) units, while for the placebo group it was 3 (range 0–13) units ($P=0.02$). In the aprotinin group, ten patients developed renal

failure and ten had respiratory complications. The corresponding figures for the placebo group were nine and 17 respectively. For survivors, the median hospital stay was 12 (range 7–33) days for the aprotinin group and 15 (range 8–52) days for the placebo group.

Conclusion: The use of high-dose aprotinin in ruptured AAA repair leads to less requirement for blood products. It does not appear to affect survival or the incidence of postoperative complications.

Outcome of 112 consecutive patients with an abdominal aortic aneurysm greater than 5.5 cm turned down for elective repair at a university hospital

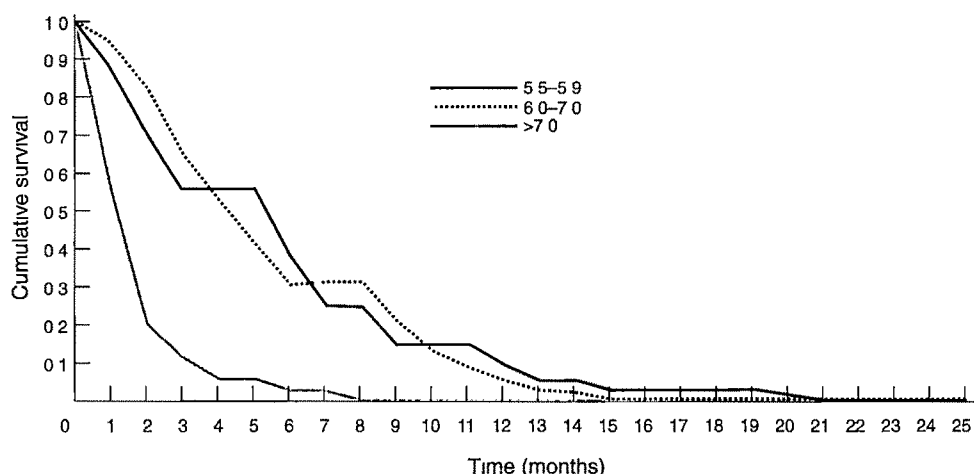
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Background: The UK Small Aneurysm study has demonstrated the low risk of rupture in aneurysms less than 5.5 cm in diameter. However, the natural history of aneurysms greater than 5.5 cm remains unresolved. Questions of equipoise probably preclude another trial in patients with an AAA over 5.5 cm. In this centre, the authors prospectively maintain records of all patients refused elective aneurysm surgery. This study aimed to document the outcome of all patients referred with an AAA greater than 5.5 cm in diameter, and to determine the cause of death and risk of rupture in all patients.

Methods: Details of all patients presenting with an AAA from 1989 to 1999 were recorded and demographic details on all patients with an AAA greater than 5.5 cm were collected. The endpoint was 1 May 1999. Copies of death certificates for deceased patients were obtained from the Office of National Statistics, local in-hospital patient records and general practitioner records. Results of post-mortem examinations were also retrieved. Aneurysms were stratified according to size at presentation (5.5–5.9, 6.0–7.0, more than 7.0 cm) and reasons for non-intervention were documented.

Results: Some 112 patients were turned down over 10 years (11.4 per year). The mean (s.d.) age of this patient group was 77.7 (7.7) years; there were 74 men and 38 women. Crude mortality data are shown in the Fig. below (Kaplan–Meier



curve). At the end of the study period, 87 patients (76 per cent) were dead, 26 (30 per cent) from a ruptured AAA. Mean survival times were: 23 months (5.5–5.9 cm), 20 months (6.0–7.0 cm) and 15 months (greater than 7.0 cm).

Conclusion: While recognizing the problems with death certification, rupture still seems to be a significant cause of death in patients with untreated AAAs greater than 5.5 cm. While little difference is observed in 5.5–7.0-cm range, patients with an AAA greater than 7.0 cm seem to have a much poorer prognosis.

Effect of propranolol on the expansion of abdominal aortic aneurysms: a randomized study

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Background: This study investigated whether propranolol reduces the growth rate of small screen-detected abdominal aortic aneurysms (AAAs).

Methods: This was a prospective blinded randomized study of men with an aneurysm between 3 and 4.5 cm detected in a community-based screening programme.

Results: Some 477 patients were randomized: 256 to take propranolol 40 mg and 221 controls. The mean growth rate in the propranolol group was 0.06 (95 per cent confidence interval 0–0.14) *versus* 0.1 (0.02–0.19) mm in the control group ($P=0.48$). Propranolol decreased growth in 59 patients with an AAA larger than 3.9 cm (0.13 (0–0.31) *versus* 0.43 (0.26–0.60) mm in controls; $P=0.02$). Compliance with propranolol treatment was poor: 31 per cent of the active treatment group were on beta blockers compared with 15 per cent in the control group. The growth in patients actually taking beta blockers was 0.24 (0.11–0.38) *versus* 0.25 (0.17–0.33) mm ($P=0.91$). Stiffness measurements did not differ significantly between patients taking beta blockers and controls. Subgroup analysis showed an increased stiffness in the patients on beta blockers (mean(s.d.) 31.1(4.2) *versus* 23.4(1.9) in controls in aortas larger than 3.4 cm; $P=0.057$).

Conclusion: Propranolol is not associated with a significant reduction in the growth of small aneurysms. Propranolol reduces the growth of aneurysms larger than 4 cm. Compliance with propranolol treatment for small aneurysms is low. Treatment of small screen-detected aneurysms with propranolol cannot be recommended.

Influence of sex on the outcome of ruptured abdominal aortic aneurysm

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Background: Mortality rates from ruptured abdominal aortic aneurysm (AAA) in men and women were compared.

Methods: Patients were identified from a population-based database using the relevant ICD-9-CM codes and were divided into three groups for analysis: those dying without admission to hospital, those admitted to hospital with ruptured AAA but not undergoing surgery, and those who underwent surgery for ruptured AAA.

Results: Ruptured AAA occurred in 648 men and 225 women over the age of 55 years during the decade 1985–1994. The proportion of women increased with age from 13.8 per cent for those aged 60–69 years, to 42.3 per cent for those over 80 years of age. Only 49.7 per cent of women (112 of 225), compared with 58.9 per cent of men (382 of 648), with ruptured AAA were admitted to hospital ($\chi^2=5.35$, $P=0.02$). Of those admitted to hospital, only 36.6 per cent of women (41 of 112) underwent surgery compared with 63.3 per cent of men (242 of 382) ($\chi^2=8.71$, $P=0.003$). The mortality rate in women undergoing surgery was 44 per cent (18 of 41) compared with 34.7 per cent (84 of 242) in men ($\chi^2=5.35$, $P=0.021$). The overall mortality rate from ruptured AAA was 89.8 per cent in women (202 of 225) and 75.6 per cent in men (490 of 648) ($\chi^2=50.34$, $P<0.0001$). Although women were on average older than men, age-specific analysis showed that this unfavourable pattern occurred in all age groups.

Conclusion: Women with ruptured AAA are more likely to die than men. The cause of the poor outcome in women is unclear but may be due to the use of thresholds for intervention that are based on aortic diameters in men.

Differential expansion rates of small abdominal aortic aneurysms between the apolipoprotein E genotypes

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Background: Carriers of the E4 allele for the gene encoding apolipoprotein E (apoE) have an increased risk of atherosclerosis. The distribution of apoE genotypes among men with a small abdominal aortic aneurysm (AAA) was compared with that among healthy men, and any differences between the genotypes in aneurysm expansion measured over 2–4.5 years were examined.

Methods: The patients originate from a population ultrasonographic screening programme with about 4800 participating 65–73-year-old men in a defined geographical region. Of 191 patients diagnosed, 57 of 77 who have been followed for 2 years or more were genotyped. Aneurysm expansion rates were determined from linear regression of diameter *versus* time of examination. The influence of apoE genotype on expansion rate was analysed using analysis of variance, with initial aneurysm size and smoking status as covariates.

Results: The E4E4 genotype was not seen among patients with an AAA, whereas three patients had the rare E2E4 genotype. These patients had higher expansion rates than patients with the common genotype E3E3 ($P=0.009$), whereas patients with the genotype E3E4 had lower rates ($P=0.034$) (see Table over).

Genotype	Population study*	AAA study*	Aneurysm expansion rate (mm year ⁻¹)†
E2E2	6 (1)	0 (0)	—
E2E3	59 (13)	6 (11)	2.9(1.8)
E3E3	252 (55)	31 (54)	2.1(1.4)
E3E4	116 (25)	17 (30)	1.4(0.9)
E4E4	18 (4)	0 (0)	—
E2E4	9 (2)	3 (5)	4.3(1.3)
Total	460	57	2.1(1.4)

*Values in parentheses are percentages, †values are mean(s.d.)

Conclusion: The findings suggest that the common polymorphism of the apoE gene influences the prognosis in patients with a small AAA. As regards the E3E4 genotype, the findings are unexpected, when compared with the known influence of E4 on the risk of atherosclerosis. This may partly explain the familial tendency of AAA, and inconsistent finding of coexisting atherosclerosis in patients with AAA. However, an impact of selection bias, due to differential survival or referral to surgery of patients with AAA, cannot be excluded.

Patch angioplasty reduces morbidity and restenosis following carotid endarterectomy

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Background: The role of patch angioplasty in the prevention of stroke and restenosis following carotid endarterectomy remains controversial, partly because of confounding variables such as surgical expertise and selective shunting.

Methods: A consecutive series of 177 carotid endarterectomies performed on 168 patients by, or under the supervision of, one surgeon between December 1992 and July 1999 with routine shunt insertion and completion arteriography was studied. Until April 1997 arteriotomies were closed primarily, with patch angioplasty reserved for small vessels or patients found to have occlusion of the internal carotid artery at operation. After April 1997 Dacron patch closure was performed routinely. All patients had duplex ultrasonography 3 months following endarterectomy.

	Primary closure (n = 117)	Patch closure (n = 60)
Wound infection	2 (2)	2 (3)
Transient ischaemic attack	1 (1)	1 (2)
Stroke	4 (3)	1 (2)
Death	3 (3)	0
Stroke or death	6 (5)	1 (2)
Restenosis > 60% at 3 months	5 (4)	1 (2)

Values in parentheses are percentages

Results: The indication for surgery and patient characteristics were similar in those who had primary closure and those with patch angioplasty. The postoperative morbidity and incidence of restenosis is shown in the *Table*.

One of two patients found at surgery to have a recently occluded internal carotid artery had a stroke. The only patient with patch angioplasty and postoperative reocclusion had the lupus anticoagulant and reported amaurosis. Two wound infections overlying Dacron patches resolved with antibiotics and there were no episodes of patch disruption.

Conclusion: This study provides further evidence that patch angioplasty following carotid endarterectomy may reduce postoperative morbidity and early restenosis.

Risk factors for aneurysm rupture: results from the UK small aneurysm study and trial

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Background: The UK Small Aneurysm Trial has shown that ultrasonographic surveillance is a safe management option for patients with small abdominal aortic aneurysms (4.0–5.5 cm in diameter), with an annual rupture rate of 1 per cent. In this study risk factors associated with aneurysm rupture have been investigated using both patients randomized into the UK Small Aneurysm Trial and those monitored for aneurysm growth in the associated study.

Methods: The cohort of patients included 1090 from the trial and 1167 from the associated study. In this cohort of 2257 patients (79 per cent men), aged 59–77 years, 103 instances of abdominal aortic aneurysm rupture were identified during the 7-year follow-up (1991–1998). The relationship between rupture and ten prespecified risk factors (including age, sex, aneurysm diameter, smoking status, plasma cholesterol, lung function and ankle: brachial pressure index) was investigated using Kaplan–Meier survival and Cox regression analysis.

Results: Almost all patients (98 per cent) had initial aneurysm diameters in the range 3–6 cm and the majority of ruptures (76 per cent) occurred in patients with aneurysms known to be larger than 5 cm in diameter. Kaplan–Meier survival and Cox regression analysis were used to identify baseline risk factors associated with aneurysm rupture. After 3 years, the annual rate of aneurysm rupture was 2.2 (95 per cent confidence interval 1.7–2.8) per cent. The risk of rupture was independently and significantly associated with female sex ($P < 0.001$), larger initial aneurysm diameter ($P < 0.001$), lower FEV₁ ($P = 0.004$), current smoking ($P = 0.01$) and higher mean blood pressure ($P = 0.01$). Age, body mass index, serum cholesterol concentration and ankle: brachial pressure index were not associated with an increased risk of aneurysm rupture.

Conclusion: Within this cohort of patients women had a threefold higher risk of aneurysm rupture than men. Effective control of blood pressure and cessation of smoking are likely to diminish the risk of rupture.

Comparison of the effect of primary and recurrent varicose vein surgery on symptoms and quality of life

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Background: Surgeons are being increasingly asked to justify interventions for primary and particularly recurrent varicose veins (VVs). The effect of primary and recurrent VV surgery on disease-specific and generic quality of life (QoL) was compared.

Methods: This was a prospective study of 251 consecutive patients. Aberdeen VV symptom severity score (AVSS) (disease-specific) and Short Form 36 (SF-36) (generic) QoL questionnaires were completed before, and 4 weeks and 6 months after operation. Statistical analysis was by non-parametric methods.

Results: Some 77 per cent of patients with primary VVs ($n = 130$) and 74 per cent with recurrent VVs ($n = 67$) completed three questionnaires. Before operation, patients with recurrent VVs had significantly worse (higher) disease-specific QoL (median (interquartile range (i.q.r.)) AVSS 22.1 (14.6–29.7) *versus* 17.0 (11.3–24.5); $P = 0.004$) than those with primary VVs. At 4 weeks, the AVSS had only improved significantly in the primary group, but at 6 months was significantly improved in both primary (7.6 (3.1–14.7); $P = 0.001$) and recurrent (13.1 (7.8–19.5); $P = 0.001$) groups. Before operation, SF-36 emotional role (median (i.q.r.)) 100 (33–100) *versus* 100 (100–100); $P = 0.016$) and vitality (58 (40–75) *versus* 65 (50–80); $P = 0.026$) were also significantly worse (lower) in the recurrent group. At 6 months, there was a significant improvement in bodily pain in both groups (primary 74 (51–100) *versus* 84 (62–100), $P = 0.001$; recurrent 62 (41–100) *versus* 74 (51–100), $P = 0.007$); and in physical functioning (85 (64–95) *versus* 93 (70–100); $P = 0.001$) and physical role (100 (50–100) *versus* 100 (94–100); $P = 0.003$) in patients with primary VVs.

Conclusion: Surgery for primary and recurrent VVs confers a highly significant improvement in disease-specific and, to a lesser extent, generic QoL.

Risk factors for delayed healing and long-term recurrence in chronic venous leg ulcers

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Background: This study aimed to identify risk factors for delayed healing and increased recurrence of chronic venous leg ulcers.

Methods: Some 669 patients with chronic leg ulcers were assessed at a one-stop clinic over the 4 years to July 1999. Possible risk factors and venous reflux patterns, assessed with colour duplex, were recorded prospectively for each patient. Some 633 legs with an ankle-brachial pressure index greater than 0.85 were treated with weekly four-layer bandaging until healed, followed by class 2 compression stockings and regular follow-up. Patients with isolated superficial venous reflux were offered surgery.

Results: Cox regression analyses of possible risk factors are summarized in the *Table* below.

Conclusion: Age, ulcer chronicity and reflux in the popliteal vein are independent risk factors for delayed ulcer healing. Delayed ulcer healing and rheumatoid arthritis are independent risk factors for ulcer recurrence. Legs with surgically corrected superficial venous reflux are relatively protected from ulcer recurrence.

Relationship between lower limb symptoms and patterns of deep and superficial venous reflux on duplex ultrasonography

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Risk factor	Delayed healing rate		Increased 3-year recurrence rate	
	Hazard ratio	P	Hazard ratio	P
Age	0.98 (0.97–0.99)	<0.001*	1.02 (1.00–1.04)	<0.05
Sex	0.98 (0.80–1.22)	n.s.	1.15 (0.76–1.72)	n.s.
Mobility score	1.09 (0.97–1.24)	n.s.	0.97 (0.78–1.19)	n.s.
Rheumatoid arthritis	1.12 (0.80–1.60)	n.s.	2.26 (1.31–3.90)	<0.005*
Diabetes mellitus	0.99 (0.68–1.43)	n.s.	1.09 (0.57–2.10)	n.s.
Ulcer size	0.99 (0.99–1.01)	n.s.	1.15 (0.76–1.72)	n.s.
Ulcer chronicity	0.99 (0.99–1.00)	<0.001*	1.00 (0.10–1.01)	n.s.
Ulcer healing time			1.01 (1.00–1.03)	<0.05*
Superficial venous reflux				
With surgery	1.04 (0.68–1.60)	n.s.	0.34 (0.17–0.69)	<0.005*
No surgery	1.21 (0.77–1.90)	n.s.	0.69 (0.34–1.38)	n.s.
Deep venous reflux	0.74 (0.43–1.28)	n.s.	0.57 (0.22–1.51)	n.s.
Mixed venous reflux	0.90 (0.60–1.37)	n.s.	0.64 (0.35–1.18)	n.s.
Popliteal vein reflux	0.73 (0.60–0.91)	<0.005*	2.80 (1.01–7.76)	0.05

Values in parentheses are 95 per cent confidence intervals. *Independent risk factors on subsequent multivariate analysis

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Background: There are inconsistent and sex-dependent relationships between lower limb symptoms and the presence and severity of trunk varicose veins on clinical examination. The relationship between lower limb symptoms and patterns of venous reflux on duplex ultrasonography were investigated.

Methods: This was a cross-sectional study of an age-stratified random sample of 1566 subjects (699 men and 867 women) aged 18–64 years selected from 12 family practices. Subjects completed a self-administered questionnaire regarding symptoms (heaviness/tension, a feeling of swelling, aching, restless legs, cramps, itching, tingling) and underwent duplex ultrasonographic examination of both legs. Reflux greater than 0.5 s was considered pathological.

Results: Isolated superficial reflux was significantly related to the presence of heaviness/tension ($P < 0.025$, both legs) and itching ($P = 0.002$, left leg only) in women. Isolated deep venous reflux was not significantly related to any symptom in either leg in either sex. Combined superficial and deep reflux was related to a feeling of swelling ($P = 0.02$, both legs), cramps ($P < 0.005$, left leg only) and itching ($P < 0.005$, left leg only) in men, and aching ($P = 0.03$, right leg only) and cramps ($P = 0.026$, left leg only) in women.

Conclusion: Duplex ultrasonography may be superior to clinical examination alone in identifying patients whose lower limb symptoms are truly of venous origin and thus most likely to benefit from surgery.

Lower limb ulceration: a detailed study of aetiology in 555 patients

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Background: The purpose of the study was to investigate the aetiology of lower limb ulceration.

Methods: The aetiology of lower limb ulceration was reviewed in 555 patients with 689 ulcerated limbs referred to a single-visit leg ulcer clinic.

Results: The mean age of the patients was 70 (range 27–95) years and 335 (60 per cent) were women. The aetiology of the ulceration in 689 limbs was venous in 496 (72 per cent), arterial in 14 (2 per cent), mixed venous and arterial in 101 (15 per cent), with other causes in 78 (11 per cent). Of the 496 venous ulcers, 261 (53 per cent) had isolated superficial reflux, 233 (47 per cent) had deep venous reflux, of which 165 (71 per cent) had full-length and 68 (29 per cent) segmental reflux, and two patients had isolated perforator reflux. Deep venous obstruction was present in 16 limbs (3 per cent) with venous ulcers and 14 of these demonstrated continuous flow in the long saphenous vein (LSV). Of the 261 ulcerated legs with isolated superficial reflux, 197 (75 per cent) had LSV reflux

only, 22 (8 per cent) had short saphenous vein (SSV) reflux only and 41 (16 per cent) had combined LSV and SSV reflux. Of those with LSV reflux, 65 per cent had a medial malleolar ulcer and 20 per cent had a lateral malleolar lesion. Of those with SSV reflux, 62 per cent had a lateral malleolar ulcer and 38 per cent had a medial malleolar ulcer.

Conclusion: Half of the ulcerated legs have superficial venous reflux; these combined with the superficial and segmental deep venous reflux group comprise the 65 per cent of patients who may benefit from superficial venous surgery. Continuous flow in the LSV should alert the clinician to deep venous obstruction, in which circumstance compression therapy should be used with extreme caution. Duplex is central to the investigation of the ulcerated leg.

Surgery reduces long-term recurrence rate in chronic venous leg ulcers

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Background: Surgical correction of isolated superficial venous reflux in ulcerated legs reduces short-term recurrence rates but little is known about long-term recurrence. This study aimed to assess the influence of venous reflux pattern and appropriate surgical correction on ulcer healing and long-term recurrence.

Methods: Patients with chronic leg ulcers were assessed prospectively at a one-stop clinic over 4 years to July 1999. Patients with an ankle: brachial pressure index (ABPI) greater than 0.85, including those with diabetes mellitus and rheumatoid arthritis, were treated with weekly four-layer bandaging in community leg ulcer clinics. Venous duplex studies in all ulcerated legs assessed venous reflux pattern and patients with isolated superficial reflux were offered surgery. Patients were advised to wear class 2 elastic compression stockings after healing and were reviewed at 1, 3, 6 and 9 months, and at 1, 2 and 3 years. Ipsilateral ulceration following healing was designated as recurrence.

Results: Some 766 ulcerated legs in 689 patients were assessed, 633 legs had an ABPI greater than 0.85. Venous duplex assessment revealed 8 per cent of these legs to have pure deep, 38 per cent pure superficial and 43 per cent a mixed reflux pattern. Ten per cent of legs had no demonstrable reflux. Some 131 of 241 limbs with pure superficial reflux underwent surgery. Healing rates at 12 and 24 weeks for all legs with an ABPI greater than 0.85 were 48 and 68 per cent respectively. Neither venous pattern nor surgery affected ulcer healing rates. Overall 1-, 2- and 3-year recurrence rates for venous ulcers were 25, 31 and 38 per cent respectively. The influence of venous reflux pattern and surgery on ulcer recurrence is summarized in *Table*.

Venous reflux pattern	No. of healed legs	Recurrence rate (%)		
		1 year	2 year	3 year
Superficial incompetence + surgery*	111	14	20	26
Superficial incompetence + no surgery*	82	28	30	44
Mixed deep and superficial incompetence	195	28	36	40

* $P=0.029$; Kaplan-Meier life-table analysis

Conclusion: Ulcer healing rates are not influenced by venous reflux pattern or surgery. Surgical correction of superficial venous reflux in the presence of chronic leg ulceration reduces long-term ulcer recurrence rates.

Thromboembolic events after carotid endarterectomy are not prevented by aspirin, but are due to the platelet response to adenosine 5'-diphosphate

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Background: Aspirin therapy fails to prevent a number of postprocedural thrombotic events, yet it still remains the standard antiplatelet regimen in most vascular surgical centres. After carotid endarterectomy (CEA), thrombosis of the endarterectomized vessel is preceded by increasing numbers of microemboli that can be detected with transcranial Doppler (TCD). The number and rate of emboli is highly predictive of thrombotic stroke. It was hypothesized that a preoperative test of platelet function might identify the mechanism(s) underlying post-CEA thrombosis.

Methods: Blood was taken from 120 patients using a standardized phlebotomy technique. Platelet fibrinogen binding was measured by whole blood flow cytometry, in unstimulated samples, and in response to adenosine 5'-diphosphate (ADP) (10^{-5} – 10^{-7} mol l⁻¹) and thrombin (0.02–0.16 units ml⁻¹). Platelet aggregation was measured using ADP (4 – 20×10^{-7} mol l⁻¹). The ability of aspirin to inhibit platelets was assessed by the aggregation induced by arachidonic acid. For the first 3 h after operation, the number of emboli occurring was quantified using TCD.

Results: Of the 120 patients studied, 110 were monitored by TCD. These were divided into patients with more than 25 postoperative emboli ($n=22$) and those with fewer than 25 emboli ($n=88$). The degree of platelet inhibition induced by aspirin was not significantly different between the two groups ($P=0.89$). However, platelets from the group with high rates of embolization bound 58 per cent more fibrinogen on flow cytometry in response to stimulation with a physiological dose of ADP (10^{-7} mol l⁻¹) ($P=0.006$). Aggregation of platelets from this group was also increased in response to ADP (35 per cent) relative to the group with few emboli ($P=0.001$). ADP also

induced more rapid aggregation in the patients with more than 25 emboli ($P=0.04$). There was no difference in the activity of resting platelets ($P=0.4$) or platelets stimulated by thrombin ($P=0.43$), between the two groups of patients.

Conclusion: These data suggest that it is the platelet response to ADP which is important in arterial thrombotic complications rather than products of the cyclo-oxygenase pathway. This observation could have significant therapeutic implications for other vascular or interventional procedures in which the endothelium is disrupted.

Putting your heart into walking further

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Background: Leg exercise training improves maximum walking distance (MWD) in claudicants, but it also causes neutrophil activation and may, as a consequence, elicit damage to the coronary circulation. It was hypothesized that symptomatic improvements induced by exercise programmes result from systemic cardiovascular effects rather than localized changes in the lower limb. The aim of this study was to develop an upper body training programme that would enhance cardiovascular fitness while avoiding potentially damaging inflammatory responses.

Methods: Sixty-three stable claudicants were recruited; all underwent arm and leg ergometry exercise assessments. Peripheral blood was obtained before and 1 h after exercise. The intensity (median channel of fluorescence; MCF) of neutrophil CD11b expression (as a measure of neutrophil activation) was determined using whole blood flow cytometry. Patients were randomized to an arm ($n=24$) or leg ($n=24$) training programme structured to achieve identical heart rate changes. Training involved two supervised sessions per week for 6 weeks. Controls undertook no exercise ($n=15$). The MWD was determined at the beginning and end of training.

Results: Arm exercise had no effect on neutrophil expression of CD11b, whereas expression was significantly increased by leg exercise (*Table*). Arm and leg training increased the maximum work rate from 75 to 100 W ($P=0.004$; Wilcoxon test) and there was a concomitant decrease in the submaximal heart rate (arm group 150 to 131 beats min⁻¹; leg group 155 to 136 beats min⁻¹; $P=0.002$). These cardiovascular changes were accompanied by an increased MWD (*Table*). There were no changes in the control group.

	CD11b (MCF)		MWD (m)	
	Before exercise	After exercise	Before training	After training
Arm	43 (34–71)	37 (31–68)	261 (188–340)	393 (335–450)*
Leg	41 (35–62)	71 (51–98)†	231 (200–341)	357 (275–430)*

Values are median (interquartile range). * $P=0.001$, † $P=0.01$ versus before training or exercise (Wilcoxon signed rank test)

Conclusion: Upper body training can increase walking distance in claudicants without neutrophil activation and maximizing cardiovascular fitness appears to be the key to improving symptoms in these patients.

In major limb vessel trauma, reperfusion injury is increased by delayed venous reflow and prevented by antioxidant pretreatment

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Background: Clinical experience of the early use of intraluminal shunts in major limb trauma at this centre aimed at restoring arterial inflow and venous outflow has been shown to reduce amputation rates and morbidity. In a model of combined arterial and venous limb vessel trauma, ischaemia-reperfusion injury caused by delayed restoration of venous drainage locally on skeletal muscle and remotely on lung was studied. Furthermore, using antioxidant pretreatment the possibility of reversing these detrimental effects was investigated.

Methods: New Zealand white rabbits ($n = 36$) were randomized into six groups: (1) sham operation; unilateral hind limb arterial and venous occlusion for 1 h followed by (2) no reflow for 2 h; (3) arterial and venous reflow for 2 h; (4) arterial reflow alone for 2 h; (5) arterial reflow for 1 h followed by arterial and venous (delayed) reflow for a further 1 h; (6) pretreatment with an enteral combination antioxidant before combined arterial and venous occlusion with delayed venous reflow. Plasma hydroperoxide (HPO) concentration in the femoral vein was a measure of lipid peroxidation. Hindlimb skeletal muscle and lung wet-to-dry weight ratio reflected tissue oedema, and myeloperoxidase (MPO) tissue levels estimated neutrophil sequestration. Plasma glutathione peroxidase (GPx) levels in systemic vein (SV) and femoral vein effluent (FV) reflected antioxidant status. Hindlimb skeletal muscle injury was graded histologically.

Results:

Conclusion: In combined major arterial and venous vessel injury of the limb, delayed venous repair leads to significantly greater local skeletal muscle injury and remote neutrophil-mediated lung damage. Reversal of these detrimental effects with antioxidant pretreatment suggests that failure of antioxidant scavenging systems may be central to the injury accentuated by delayed venous drainage. These results support the clinical rationale for early restoration of not only arterial inflow but also venous drainage by intraluminal shunts.

Protease expression in human aneurysmal and occlusive atherosclerotic aortas

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Background: Atherosclerosis is implicated in the pathogenesis of abdominal aortic aneurysm (AAA), yet often causes aortic occlusive disease (AOD). Proteolysis of elastin and collagen, the major structural proteins of the aortic wall, must occur for an aneurysm to dilate. The matrix metalloproteinases (MMPs) are a class of enzymes that degrade elastin and collagen in the extracellular matrix and are believed to play a central role in the pathogenesis of AAA. However, some MMPs have also been found in atherosclerotic occlusive disease, in the absence of dilating disease. Differences in the expression of MMPs may determine whether an atherosclerotic aorta dilates or occludes. The expression of MMPs and their natural inhibitors (TIMPs) in human abdominal aortic aneurysm and stenosing atherosclerotic aortas was measured.

Methods: Samples of aortic wall were obtained from eight patients with AAA and eight with AOD. Expression of the MMPs was estimated with the reverse transcription polymerase chain reaction using a synthetic multicompeter standard as a robust internal control. The standard allowed assay of 14 MMPs and three TIMPs.

Results: AAA wall expressed significantly more of the collagenolytic enzyme stromelysin 1 (MMP-3) and TIMP-3 than AOD wall (stromelysin 1: mean(s.d.) log (MMP-3/GAPDH) – 1.97(0.52) in AAA versus – 3.36(0.77) in AOD, $P < 0.01$; TIMP-3: – 1.79(0.69) versus – 2.84(0.78), $P < 0.01$). The elastolytic enzymes matrilysin, macrophage metalloelastase (MMP-7 and MMP-12), gelatinases 2 and 9, and membrane-type metalloproteinase 1 were expressed in both AAA and AOD.

	Femoral vein HPO ($\mu\text{mol l}^{-1}$)	GPx (units l^{-1})			Lung MPO (units g^{-1})	Skeletal muscle histological injury grade
		SV start	SV end	FV end		
1	1.0(0.1)	414.9(31.7)	391.4(33.4)	440.1(47.2)	1.7(0.1)	None
2	1.8(0.5)	291.7(10.9)	363.2(62.4)	488.6(45.6)	2.3(0.2)	None
3	1.2(0.4)	423.1(68.3)	398.6(63.9)	409.1(63.9)	2.4(0.2)	Mild
4	1.7(0.3)	408.8(26.4)	399.0(35.4)	397.3(26.4)	1.9(0.2)	Moderate
5	2.0(0.5)*	468.0(40.8)	412.2(35.6)	358.4(22.0)	3.2(0.3)‡	Severe
6	0.9(0.2)	607.9(36.3)†	562.3(40.7)†	547.2(24.9)†	2.1(0.3)	Mild

Values are mean(s.e.m.). * $P < 0.05$ versus groups 1, 3 and 6, † $P < 0.01$ versus groups 1–5, ‡ $P < 0.05$ versus group 1

Conclusion: There is expression of most elastolytic and collagenolytic MMPs in both aneurysms and occlusive disease, but expression of stromelysin 1 is greatly increased in aneurysms. Stromelysin 1 may be responsible for collagen breakdown in aneurysm disease and provide a target for pharmacological intervention.

Smoking, cadmium accumulation and aortic aneurysm

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Background: Smoking is an important risk factor for abdominal aortic aneurysm (AAA), a disorder associated with loss of medial smooth muscle cells. Cadmium, one of the toxic components inhaled in cigarette smoke, is known to alter the metabolism of aortic smooth muscle cells. This was an investigation of the hypothesis that excess cadmium accumulation in the abdominal aorta is associated with the development of aneurysms.

Methods: Samples of abdominal aorta were obtained at the time of surgery from 12 patients with AAA (seven men and five women, mean age 72 years) and at autopsy from 17 patients (ten men and seven women, mean age 76 years) with an undilated aorta (diameter 1.6–2.2 cm). The smoking history of all patients was noted. The aorta was dissected into three layers, intima, media and adventitia; each was dried to a constant weight, hydrolysed and cadmium was measured by atomic absorption spectrometry. In separate experiments 5-bromo-2'-deoxyuridine uptake and picogreen assay of DNA were used to investigate the effect of cadmium on the proliferation of cultured aortic smooth muscle cells.

Results: The mean (s.e.) cadmium content of the intima, media and adventitia was 1.14(0.24), 3.25(0.53) and 1.87(0.38) ng per mg dry weight respectively; the medial concentration was significantly higher than the concentration in the other two layers ($P < 0.005$). The medial cadmium content was similar in AAA and normal diameter aortas: 3.65(1.00) and 2.97(0.59) ng per mg dry weight respectively. Only trace amounts of cadmium were present in the aorta of those who had never smoked and there was a strong positive association between medial cadmium content and pack-year history of smoking ($r_s = 0.87$, $P < 0.001$). Cadmium inhibited the proliferation of smooth muscle cells cultured on polymeric collagen, 5-bromo-2'-deoxyuridine uptake (IC_{50} 1.4 nmol l⁻¹) and DNA content (IC_{50} 6.3 nmol l⁻¹). Cadmium was less toxic, by more than tenfold, to smooth muscle cells cultured on fibronectin, monomeric collagen or plastic.

Conclusion: Cadmium accumulates selectively in the medial layer of the abdominal aorta of smokers, where it may inhibit DNA synthesis and proliferation of smooth muscle cells. The toxic effects of cadmium on cultured smooth muscle cells depend on their underlying matrix and this may explain why the accumulation of cadmium in aortic media was not associated with the development of aneurysms.

Decreased endothelin binding and receptor density in varicose veins

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Background: The primary cause of venodilatation and reduced contractility in varicose veins is unclear. Endothelin (ET) 1 acts on smooth muscle cell ETA/ETB receptors to induce contraction and growth, and on endothelial cells to induce production of the vasorelaxant and growth inhibitors nitric oxide and prostacyclin. These factors may be involved in the aetiology of varicose veins. This study investigated ET-1 binding and ETA/ETB receptor density in varicose and non-varicose veins.

Methods: Proximal long saphenous vein (LSV) sections from nine patients undergoing surgery for varicose veins were compared with normal LSV from nine patients undergoing coronary artery bypass surgery. Slide-mounted sections were incubated in [¹²⁵I]-radiolabelled ET-1 and ETA/ETB binding sites were identified using subtype-selective radioligands. Receptor density and distribution was quantified on autoradiographs by densitometry and binding was localized at the cellular level by nuclear emulsion.

Results:

	ET-1 ($\times 10^{-3}$ d p m mm ⁻²)	ETA receptor ($\times 10^{-3}$ d p m mm ⁻²)	ETB receptor ($\times 10^{-3}$ d p m mm ⁻²)
Varicose veins (n=9)	18.08(2.38)	5.13(0.42)	2.12(0.55)
Controls (n=9)	24.83(1.72)	5.72(0.71)	3.72(0.45)
P*	0.04	0.48	0.03

Values are mean (s.e.) radioligand binding *Unpaired *t* test

ET-1 binding and ETB receptor density decreased significantly in the varicose group. There was no significant difference in ETA receptor density.

Conclusion: Decreased ET-1 binding may contribute to venodilatation and poor contractility in varicose veins. This may be due to decreased tunica media ETB receptor density.

Methicillin-resistant *Staphylococcus aureus* infection in vascular patients

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Background: The increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is a major threat in arterial surgery and poses a considerable therapeutic challenge. The

aim of this study was to assess the prevalence of MRSA infection in patients treated in the vascular unit.

Methods: A retrospective case-note review was undertaken to identify the nature of the infection and the outcome.

Results: During 1993–1998, a total of 115 patients (4 per cent of the total) were positive for MRSA. Of these, 67 were colonized and 48 were infected by MRSA. The number of MRSA infections increased yearly (1 per cent in 1994 to 5 per cent in 1998). Of the 48 patients infected by MRSA, one had wound infection following brachial embolectomy which eventually resolved. Two patients had undergone carotid endarterectomy necessitating removal of an infected Dacron patch, one of whom developed a hemiparesis. Eleven patients had undergone elective abdominal aortic aneurysm (AAA) repair (five developed pneumonia, two septicaemia, two wound infection, one a false aneurysm at the site of insertion of an endovascular stent, and one developed crossover graft infection after endovascular AAA repair and died). Five patients had undergone ruptured AAA repair (two developed pneumonia, one wound infection and two developed graft infection and died). Four patients undergoing reconstruction for aortic occlusive disease developed MRSA infection, two of whom died. Twenty-five patients with MRSA infection had undergone lower limb procedures. Five of these had graft infection leading to amputation in three and death in two. One patient developed primary arterial infection following embolectomy resulting in arterial rupture.

Conclusion: These results suggest that the prevalence of MRSA infection in vascular patients is increasing. Infection of aortic grafts appears to be uniformly fatal and lower limb graft infection is associated with a high rate of limb loss.

Prospective, multicentre audit of complex vascular wound and graft infections: the impact of methicillin-resistant *Staphylococcus aureus*

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Background: A number of studies have looked at the outcome of vascular graft infections, but these often include small numbers of patients collected over a prolonged period of changing practice. Many of these studies do not contain cases of methicillin-resistant *Staphylococcus aureus* (MRSA).

Methods: Between February 1998 and January 1999, a prospective, multicentre audit was performed in order to examine the outcome of complex wound and graft infections in vascular surgery, with particular reference to MRSA.

Results: Some 66 grade II or III Szilagyi wound infections occurred. Overall, 23 per cent of type II infections progressed to graft infection. Of those with type III infections, 83 per cent had an adverse outcome (death, major amputation or ongoing infection). No vein graft became infected, but 12 of 38 prosthetic grafts were affected. MRSA accounted for 42 per cent of infections and was present in 67 per cent of patients with

an adverse outcome. Adverse events occurred in 32 per cent of MRSA cases and in 10 per cent of non-MRSA cases ($P = 0.04$). Wound infection proceeded to graft infection in 58 per cent of MRSA cases and in 32 per cent of non-MRSA cases ($P = 0.08$). Seven of eight patients with MRSA before operation developed postoperative MRSA infection. Median length of stay was 31 days for MRSA *versus* 18 days for non-MRSA infections ($P = 0.001$). Forty-three graft infections occurred; 12 were associated with a complex wound infection. Median time to presentation was 39 (range 2–2450) days. There were 16 deaths, nine major limb amputations and three ongoing infections among patients with a graft infection. The median length of stay was 36 days. MRSA was present in 36 per cent of all graft infections. Only one of these infections involved a vein graft ($P = 0.001$). MRSA infection occurred more frequently where the primary procedure had been urgent rather than elective ($P = 0.03$). MRSA graft infection accounted for seven of the nine major limb amputations. The median length of stay in patients with MRSA graft infection was 25 days longer ($P = 0.001$).

Conclusion: Complex wound and graft infections continue to be associated with postoperative deaths and amputations. MRSA infection is now the most common organism involved in complex infections following vascular procedures. It is associated with an increase in the number of adverse outcomes and a significant increase in length of stay.

Use of superficial femoral/popliteal veins for suprainguinal arterial reconstruction in the presence of infection

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Background: Mycotic aneurysms and graft infection in the aortoiliac region provide formidable technical challenges and carry a high morbidity and mortality rate with either of the standard techniques of *in situ* antibiotic-bonded prosthetic reconstruction or extra-anatomical bypass. This study investigated the use of autologous superficial femoral/popliteal vein (SFPV) for arterial reconstruction in ten patients with arterial or graft infections of the aortoiliac region.

Methods: Two patients with mycotic aortic aneurysms and four with aortic graft infections underwent aortoiliac replacement with SFPV after thorough debridement and/or excision of infected graft material. Three infected femorofemoral grafts were replaced *in situ* with reversed SFPV and an infected axillofemoral graft was converted to an iliofemoral reversed SFPV graft. All patients received appropriate antibiotic therapy and were followed by regular postoperative duplex imaging. Preoperative femoral vein duplex imaging was performed in eight of ten patients to confirm suitability as a graft.

Results: Nine of the ten patients survived with a functioning graft and without limb loss or evidence of infection at 3–30 months. One patient died from myocardial infarction after

operation. Two patients had minor swelling of one leg. Three patients required angioplasty of anastomotic stenoses detected by duplex surveillance at 6 weeks.

Conclusion: SFPV is an excellent conduit for aortic or iliac reconstruction in the presence of infection. Duplex imaging is useful to confirm the suitability of deep veins for use as a graft and for postoperative surveillance.

Larval debridement therapy: a cost-effective alternative to hydrogel in necrotic venous ulcers: a randomized trial

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Background: Evidence for the effectiveness of larval debridement therapy (LDT) in necrotic wounds has hitherto been the anecdotal results of enthusiasts. The aim of this study was to compare the cost and effectiveness of LDT with standard hydrogel treatment of necrotic venous ulcers.

Methods: Patients with sloughy venous ulcers were randomized to either standard hydrogel dressings (Intrasite gel) (group 1) or LDT (group 2). All patients were reviewed every 72 h until effective debridement had occurred, for a maximum of 1 month. The outcome measure used for effectiveness was whether or not desloughing occurred and time to deslough. The measures of cost were the cost of nursing time, dressing costs, and costs of larvae and hydrogel required to achieve healing in 1 month's treatment.

Results: Twelve patients were randomized. Ulcers in all patients receiving LDT (group 2) desloughed within two applications of larva therapy. All of these patients were treated subsequently with four-layer bandaging and all healed within 4 months. Ulcers in only two patients in group 1 desloughed completely within 1 month. One of the patients in whom hydrogel had failed at 1 month was changed to LDT and the ulcer desloughed with one application. Taking into account the cost of a vial of larvae (£58), the overall median cost of treatment in group 1 was greater than that in group 2 (£136.23 (range 63.89–319.30) versus £78.64 (range 73.49–£92.36)).

Conclusion: LDT is more effective and significantly less expensive than hydrogel in the debridement of sloughy venous ulcers. While a larger randomized controlled study should be performed to confirm these observations, LDT appears to be a cost-effective alternative to hydrogel.

Randomized trial of rifampicin-bonded Dacron grafts for extra-anatomic vascular reconstruction: 2-year results

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Background: Serious infection complicates a small proportion of prosthetic vascular grafts and usually follows implantation of bacteria at the time of graft insertion. The aim of this study was to determine whether the use of a rifampicin-bonded, gelatin-

coated Dacron graft (Gelsoft/Gelseal; Sulzer Vascutek) could reduce the rate of infective complications after extra-anatomic bypass.

Methods: In a multicentre study involving 14 vascular units, 257 patients underwent extra-anatomic bypass. There were 178 men and 79 women, of median age 69 (range 43–92) years. Some 132 (51 per cent) had no risk factors for wound or graft sepsis, 82 (32 per cent) had one and 43 (17 per cent) had two or more risk factors. Patients were randomized to rifampicin bonding (rifampicin 1 mg ml⁻¹ soak for 15 min before insertion) ($n = 123$) or control ($n = 134$). The authors have previously reported small, but not statistically significant, reductions in total perioperative wound complications, antibiotic requirements and delayed hospital discharge in favour of patients with bonded grafts.

Results: Of 257 patients originally randomized, follow-up to 2 years or death is available for 197 patients; 60 have died. A total of ten patients have had serious wound or graft infections (Szilagyi grade III), four with unbonded and six with bonded grafts (P not significant). All occurred within 6 months of operation. The graft fabric was involved in eight patients. Treatment and outcome are listed in the Table below.

Treatment	No.	Outcome
Antibiotics	4	No amputations, one died (2 bonded and 2 controls)
Revised graft	1	Amputation, survived (control)
Graft removed	1	Amputation, survived (bonded)
Sartorius flap	1	No amputation, survived (bonded)
Died	3	After operation (1 bonded, 1 control) Systemic sepsis (bonded)

Conclusion: It has not been possible to show any advantage for the routine use of antibiotic bonding for extra-anatomic reconstruction.

Vascular Surgical Society operative outcome study: preoperative physiology predicts outcome

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Background: This was an audit of operative outcome conducted by the Vascular Surgical Society of Great Britain and Ireland (VSSGBI).

Methods: Some 121 surgeons (all members of the VSSGBI) completed data questionnaires on patients undergoing arterial surgery under their care (mean 12, range 1–49) in May and June 1998. A total of 1480 completed data records were available for logistic regression analysis using the Portsmouth modification of the Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (P-POSSUM) methodology. Information collected included all POSSUM data items plus other factors thought to have a significant bearing on patient outcome: VSSGBI 'extra items'. The main outcome measures

were death within hospital admission and major postoperative complications. The data records were checked for consistency and the remaining 1313 were divided into two sets for analysis. The first 'training' set was used to obtain logistic regression models that were applied prospectively to the second 'test' data set for various combinations of the POSSUM physiological and operative scores and the VSSGBI 'extra items' found to be significantly associated with outcome.

Results: Using POSSUM data items alone, it was possible to predict both death and morbidity after vascular reconstruction using P-POSSUM analysis. Addition of the VSSGBI 'extra items' found significant in regression analysis did not significantly improve the accuracy of prediction. The most accurate model predicting both death and morbidity was derived from the preoperative physiology components of the POSSUM data items alone.

Conclusion: P-POSSUM methodology can be used to predict outcome after arterial surgery across a range of surgeons in different hospitals and could form the basis of a national outcome audit. The most startling finding was that the preoperative physiology scores alone were predictive of both death and major morbidity after vascular reconstruction.

Carotid artery plaque instability is associated with expression of matrix metalloproteinases 2 and 12

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Background: There has been considerable interest in the role of matrix metalloproteinases (MMPs) in atherosclerotic plaque rupture and the possible use of MMP inhibitors in stabilization of plaques. Collagenolytic MMPs, although important in causing plaque instability, may not be a feasible target, as interfering with collagen turnover in tightly stenosed lesions may induce occlusion. This study investigated the expression of elastinolytic MMP-2, MMP-9 and MMP-12 in carotid plaques in relation to plaque stability.

Methods: Plaques removed at surgery were examined immediately and classified as unstable (plaques with ulceration, rupture, thrombosis; $n = 34$) or stable (plaques with or without calcification without the above complications; $n = 26$). MMP expression was studied by immunohistochemistry (after saponin permeabilization) and computed image analysis of whole plaques to obtain percentage staining.

Results: Expression of all three MMPs was significantly higher in unstable plaques.

	Staining (%)	
	Stable	Unstable
MMP-2	13.52 (1.29–24.31)	49.19 (38.00–64.83)*
MMP-9	3.01 (0.47–9.69)	37.93 (18.20–49.31)*
MMP-12	15.20 (5.64–20.09)	53.72 (38.73–64.00)*

Values are median (interquartile range). * $P < 0.0001$ versus stable (Mann-Whitney test)

In a logistic regression model, only MMP-2 ($P = 0.04$) and MMP-12 ($P = 0.0018$) expression was shown to be significantly greater in unstable plaques.

Conclusion: Although MMP-2, MMP-9 and MMP-12 are all expressed in higher amounts in unstable plaques, MMP-12 was shown to be the most significantly associated with plaque instability, followed by MMP-2. These findings may be useful in directing efforts to develop specific inhibitors, particularly to MMP-12 which has elastin and not collagen as its main substrate.

Initial management of cerebrovascular disease by general practitioners

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Background: The aim of this study was to determine the primary management of patients presenting with a new diagnosis of transient ischaemic attack (TIA) or stroke by general practitioners and to establish whether practice was uniform across the UK, and to determine whether initial management influenced the performance of carotid endarterectomy (CEA) across the health regions of the UK.

Methods: Information on regional reporting of new cases of TIA and stroke between 1992 and 1996 was obtained from the General Practice Research Database, a database of six million patients from 450 practices. Analysis of data from the primary care database and routine data sources was undertaken. Main outcome measures were incidence of TIA and stroke, rates of referral for specialist opinion, prescription of antiplatelet agents and rates of CEA.

Results: There were twofold differences ($P < 0.00005$, χ^2 test) in the incidence of cerebrovascular disease between Regional Health Authorities (RHAs) between the years 1992 and 1996 and also for each year. Mean stroke incidence per annum was 143 per 100 000 and TIA incidence 183 per 100 000. Yorkshire had the highest incidence at 170 (stroke) and 206 (TIA) per 100 000 of the population compared with 95 and 98 per 100 000 for Oxford. Some 37 per cent of new patients with stroke and 19 per cent of patients with TIA were referred for specialist opinion following initial diagnosis. These rates did not change over time. There was no positive correlation between disease incidence and referral rate; Yorkshire referred the least (14 per cent) and Oxford the most (26 per cent). The majority of referrals for TIA were made to general medicine (39 per cent), 6 per cent of patients were referred directly for surgical opinion. Mean prescription rate of antiplatelet medication over the time period was 17 per cent for patients with stroke and 35 per cent for those with TIA. Mean CEA rate for English RHAs for the time interval was 15.5 per 100 000. There was a positive correlation between the incidence of disease and rate of CEA, with the regions with the highest incidence of disease tending to perform the most CEAs.

Conclusion: The incidence of cerebrovascular disease varies significantly across health regions in the UK. There was no correlation between the regional incidence of disease and the number of patients referred for specialist opinion, but CEA rates were generally correlated with the regional difference in incidence of disease. The low referral rate may be a factor in the perceived underperformance of CEA in the UK and the low usage of antiplatelet medication is surprising.

Effect of carotid endarterectomy on cognitive function: long-term follow-up

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Background: Long-term effects of carotid endarterectomy (CEA) on cognitive function are not known. Evidence suggests that perioperative embolization may disrupt cognitive function in the short term.

Methods: A controlled study was conducted to examine the cognitive function of 109 patients undergoing CEA before and at 6 months after operation ($n = 100$). The objective validated psychometric tests assessed attention, memory, language and visuospatial skills. Perioperative embolization was determined using transcranial Doppler ultrasonography.

Results: Patients who were spontaneously embolizing before operation had significant preoperative cognitive impairment ($P = 0.03$). The controlled cognitive function tests showed no evidence of a cognitive deficit 6 months after CEA. The total number of emboli detected for each patient ranged from 0 to 700 (mean 32). There was no evidence of a significant correlation between the number of emboli detected during CEA and change in cognitive function ($r = 0.07$).

Conclusion: CEA is not associated with worsening cognitive impairment. Asymptomatic perioperative microembolization has no long-term effect on cognitive function.

Patients' understanding of risk and benefit associated with carotid endarterectomy

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Background: Recent well publicized cases have highlighted problems regarding a patient's perception of risk and the provision of informed consent which currently forms the medicolegal and ethical basis of modern healthcare practice. This study was designed to determine whether patients understood the risks of stroke associated with carotid endarterectomy (CEA).

Methods: All patients were counselled by the surgeon before going on the waiting list. Patients were informed that the risk of stroke due to surgery was 2.5 per cent and that 3 years after CEA a further 5 per cent of patients will also have suffered a

stroke. This compares with a 20–30 per cent risk of stroke at 3 years in patients treated medically. Some 71 patients on the waiting list for CEA were surveyed regarding their understanding of the risk and benefit to health of undergoing CEA. **Results:** Patients' estimates of stroke risk due to surgery ranged from 0 to 65 per cent (actual risk 2 per cent). Patients also dramatically overestimated their risk of stroke without the operation (mean 57 per cent). In addition to preventing stroke, most patients also believed that CEA would improve angina, poor memory or shortness of breath. When resurveyed the day before the operation patients' perception of risk associated with surgery had increased threefold ($P < 0.01$).

	Patients' estimate* (%)	Actual figure (%)
Risk of stroke without operation	57 (22–100)	22
Risk of stroke after CEA	24 (0–95)	8
Risk due to CEA	10 (0–65)	2

Values are mean (range) estimates 1 month after clinic

Conclusion: Most patients failed to understand the risks and benefits associated with CEA. Despite best efforts, the current doctor–patient relationship still fails to furnish patients with the skills and knowledge needed for healthcare decision making. Patients' recall of statistical data is extremely limited even in the short term.

Durability of femoropopliteal transluminal angioplasty for claudication

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Background: Some 200 consecutive femoropopliteal transluminal percutaneous angioplasties (PTAs) in patients with claudication were followed up to ascertain the long-term patency.

Methods: One hundred and forty-six patients (200 angioplasties) who underwent PTA were followed up between 1991 and 1997. Clinical symptoms, ankle:brachial pressure index (ABPI) and duplex scan assessment were recorded. Mean follow-up was 43.2 months.

Results: The median age of patients was 66 (range 49–86) years, with a mean claudication distance of 68 (range 10–274) m. Primary patency at 1, 3 and 5 years was 72, 54 and 32 per cent respectively. Stenosis rather than occlusion, ABPI greater than 0.8 after angioplasty and immediate symptomatic improvement were associated with favourable outcome. Diabetes adversely affected patency. Twenty-one patients (11 per cent) required bypass surgery following a failed PTA.

Conclusion: In contrast to some reports in recent literature, long-term patency following PTA is poor in claudicants.

Durability of angioplasty in treating severe leg ischaemia

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Background: Percutaneous transluminal angioplasty (PTA) has recently been accepted as a valuable therapeutic option in patients with severe limb ischaemia. However, despite the increasing use of this technique, there have been concerns that the long-term efficacy of PTA is inferior to that of surgical revascularization. This prospective study reports the outcome of an unselected cohort of patients who underwent balloon angioplasty for severe lower limb ischaemia in a single centre. **Methods:** During 1997, 108 patients with 133 severely ischaemic legs were treated by PTA. The median age of the patients (49 per cent men) was 76 years. Symptoms were rest pain in 31 per cent, ischaemic ulceration in 56 per cent and gangrene in 13 per cent. The distribution of risk factors was typical: diabetes 32 per cent, ischaemic heart disease 18 per cent and stroke 16 per cent. Median (interquartile range) follow-up was 16 (12–19) months. There was a mean of 1.7 angioplasty sites per patient, distributed in the iliofemoral (14 per cent), superficial femoral (42 per cent), popliteal (18 per cent) and crural (26 per cent) arteries. PTA was performed lumenally in 20 per cent of cases and subintimally in the remainder. Overall, 67 per cent of the lesions were complete occlusions with a median length of 20 (10–40) cm.

Results: Technical success was achieved in 104 limbs, with 29 failures. The outcome of patients with a failed angioplasty (29) was poor, with 14 requiring bypass surgery, 11 undergoing a major amputation and 32 per cent dying after the procedure. In contrast, patients having a technically successful angioplasty had a good outcome after a median follow-up of 16 (12–19) months. In this group there was a 30 per cent overall mortality rate during follow-up. However, 85 per cent of the patients had no symptoms of critical ischaemia and the limb salvage rate was 92 per cent.

Conclusion: PTA is an effective and durable procedure in patients with critical leg ischaemia, with results comparable to those of historical surgical controls. Technical failure of PTA is, however, associated with a dire outcome.

Complications of percutaneous transluminal angioplasty in the legs: analysis of 1379 procedures

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Background: Percutaneous transluminal angioplasty has firmly established itself as a useful adjunct to surgery in the management of patients with peripheral vascular disease. A large series has been reviewed to assess the impact of the increase in the

number of procedures performed as well as the improvements in technique on the complication rate of the procedure.

Methods: The complications of all percutaneous transluminal angioplasty procedures carried out between 2 October 1995 and 29 September 1998 were recorded and analysed prospectively.

Results: There were 1379 procedures carried out on 988 patients. There were 551 men (55.8 per cent) and 437 women (44.2 per cent), with a mean age of 62.5 years. A total of 1756 vessel segments were dilated. The indications for angioplasty included claudication (620 patients, 62.8 per cent), critical ischaemia (270, 27.3 per cent) and bypass graft complications (98, 9.9 per cent). The major complications were retroperitoneal bleed (0.2 per cent), false aneurysm (0.2 per cent), myocardial infarction (0.4 per cent), acute limb ischaemia (1.5 per cent), pulmonary embolism (0.1 per cent), renal failure (0.4 per cent), stroke and transient ischaemic attack (0.4 per cent) and respiratory failure (1.0 per cent). Minor complications were haematoma in 0.9 per cent, perforation in 1.7 per cent, wound infection in 1.0 per cent and catheter complications in 0.6 per cent. The overall rate of significant complications was 4.2 per cent and that of minor complications was 4.2 per cent. The overall incidence of complications needing surgical intervention was 2.2 per cent. The overall amputation rate due to complications was 0.6 per cent.

Conclusion: The sharp rise in the number of angioplasties in recent years has not been accompanied by a similar rise in the number of complications, despite broadening of the referral spectrum.

Prospective audit of carotid endarterectomy in Scotland

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Background: Carotid endarterectomy (CEA) is a proven means of stroke prevention provided it is performed in appropriate patients, soon after the index ischaemic event and with low perioperative morbidity and mortality rates. This study investigated how well these conditions are being met in Scotland.

Methods: This was a prospective study of all 485 CEAs performed in National Health Service hospitals between 1 September 1997 and 31 September 1998. Data collection was by four independent research nurses.

Results: The median patient age was 67 (interquartile range 61–73) years; 461 patients (95 per cent) were operated on for focal symptoms, 389 of whom had a stenosis of 70 per cent or more. Some 36 per cent of patients were seen by the operating surgeon within 2 weeks of referral and 35 per cent were operated on within 1 month thereafter. The perioperative combined major stroke and death rate was 3 per cent. Operations were performed by 30 surgeons in 13 hospitals. The number of CEAs per surgeon ranged from one to 49, with

ten surgeons undertaking fewer than ten operations. The number of CEAs per hospital ranged from four to 99 with only three surgeons undertaking more than 50 operations. The number of CEAs per hospital ranged from four to 99 with three hospitals undertaking 50 or more operations in the study period.

Conclusion: Despite the 'diffuse' nature of vascular surgical services necessitated by the demography and geography of Scotland, CEA is currently being performed with a perioperative major stroke and death rate substantially lower than that reported from randomized controlled trials. However, the overall effectiveness of surgery might be improved by reducing the delays to surgery.

Dextran-40 stimulates resting platelets and binds more avidly to activated platelets

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Background: A programme of monitoring and treatment with low-dose 10 per cent Dextran-40 (20 ml h⁻¹) can successfully prevent thrombotic occlusion of the carotid artery after endarterectomy. This is a clinically effective treatment, over 500 CEAs have been performed with no thrombotic strokes, but little is known about the mechanism by which low-dose Dextran-40 affects platelet-rich thrombus formation.

Methods: In study 1, platelets from ten patients undergoing CEA were collected in a standardized manner. The response to therapeutic doses of Dextran-40 was assessed *in vitro* using whole-blood flow cytometric analysis of fibrinogen binding in response to adenosine 5'-diphosphate (ADP) and thrombin. Platelet aggregation in response to ADP and collagen was recorded. In study 2, blood collected from ten normal subjects was incubated with fluorescently labelled Dextran-40 and binding was measured using flow cytometry. In these experiments blood was either first incubated for 10 min with the FITC-Dextran-40 and then activated with thrombin 0.4 units ml⁻¹ or activated with thrombin 0.4 units ml⁻¹ for 10 min before incubation with FITC-Dextran-40.

Results: In study 1, reincubation of the patients' blood with Dextran-40 increased fibrinogen binding to resting platelets by 352 per cent ($P < 0.05$) and to ADP-stimulated platelets by 39 per cent ($P < 0.05$). Dextran-40 also increased fibrinogen binding in response to thrombin although this difference was not significant ($P = 0.12$), and increased platelet aggregation in response to ADP (48 per cent) and collagen (32 per cent) ($P < 0.05$ for both). In study 2, fluorescently labelled Dextran-40 bound to the surface of resting platelets from normal subjects in a dose-dependent manner, and caused platelet activation, as measured by increased P-selectin expression. Incubation with Dextran followed by activation caused a 28 per cent increase in Dextran binding; however, if the platelets were activated first and then exposed to Dextran the binding increased 94 per cent ($P = 0.001$).

Conclusion: Low-dose Dextran-40 is very effective in preventing thromboembolic complications after CEA. However, *in vitro*, Dextran-40 has a direct stimulatory effect on platelets. Dextran-40 binds to platelets and shows preferential binding to activated, compared with resting, platelets. Dextran may exert a beneficial antiplatelet/antithrombotic effect *in vivo* by inhibiting the recruitment of activated platelets to a growing thrombus.

'Kissing stent' insertion is not safe or durable

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Background: The morbidity, and clinical and haemodynamic outcome of kissing stent insertion was assessed.

Methods: A prospectively gathered database of endovascular procedures performed between 1 January 1993 and 31 December 1998 was analysed.

Results: Bilateral kissing stents were deployed in 12 patients (median age 62 (range 43–67) years; five men and seven women). Indications were bilateral intermittent claudication (IC) in nine patients, unilateral IC with contralateral rest pain in two and bilateral rest pain/tissue loss in one. Major morbidity occurred in three patients and comprised bilateral distal iliac dissection (treated medically), distal embolization (thrombolysis and suction aspiration) and false aneurysm (surgical repair). All patients reported an immediate improvement in symptoms. However, at a median (range) follow-up of 27 (3–70) months, symptoms have deteriorated in 13 legs, the ankle:brachial pressure index has fallen by more than 0.15 (with respect to values immediately after the procedure) in 15 legs, six stents have occluded (bilaterally in two patients, unilaterally in two) and four stents have stenosed significantly (greater than 50 per cent). Four patients have undergone aortobifemoral grafting and one further patient has undergone bilateral amputation following failed revascularization necessitated by stent thrombosis.

Conclusion: In contrast to the single previously published series of 20 patients which found the technique to be 'effective' with 'few serious adverse events', present data suggest that kissing stents are associated with significant morbidity and a poor outcome.

Combined surgical and radiological procedures

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Background: The aim was to audit the effect of provision of an interventional theatre on the management of vascular disease in a tertiary centre.

Methods: All patients undergoing joint vascular surgical and radiological procedures during 20 months were reviewed. Data are presented with respect to type of procedure, initial success and length of hospital stay.

Results: Between October 1997 and July 1999, 100 combined procedures were performed in an endovascular operating theatre. Sixty of these were for stent-graft repair of abdominal aortic aneurysm and are excluded from further analysis. Forty patients (23 men and 17 women, of median age 65 (range 37–80) years) underwent combined procedures for claudication (nine), rest pain (13), tissue necrosis (five), acute ischaemia (seven), iliac aneurysm (three), amaurosis fugax (one), arteriovenous malformation (one) and subclavian vein occlusion (one).

Radiological procedures	n	Surgical procedures	n
Angioplasty	16	Arterial exposure only	14
Stent	18	Infrainguinal bypass	10
Embolectomy	3	Thrombendarterectomy	9
Coil embolization	4	Patch angioplasty	2
Arteriography	1	Amputation/debridement	2
Covered stent	4	No surgery performed	3

Combined intervention was successful initially in 35 patients. Of the five failures, three were technical (not possible to cross an occluded vessel) and two were due to absence of run-off vessels. There was no perioperative death. Median hospital stay was 9 (range 1–116) days.

Conclusion: These data confirm that patients requiring both radiological and surgical intervention can be treated successfully within the confines of an interventional operating suite. Cooperation and coordination between surgeon and radiologist allows the tailoring of procedures to the individual patient's needs.

Surgical management of thoracic outlet syndrome

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Background: The role of surgical decompression for thoracic outlet syndrome (TOS) is not clearly established, especially for the neurological (N-TOS) or venous (V-TOS) variants. Reports lack objective diagnostic criteria and follow-up. American series almost exclusively describe N-TOS. In the authors' practice, arterial TOS (A-TOS) is much more common. Patients are treated by a multidisciplinary team and surgery is reserved for those failing to respond to conservative measures.

Methods: Data regarding assessment, diagnosis (clinical, radiology, electromyography, duplex) are collected prospectively on a database (Paradox). Independent follow-up has categorized surgical results by structured questionnaire.

Results: Of 129 patients (104 women; median age 37 years), 91 underwent transaxillary first rib resection (50 A-TOS, 31 N-TOS, ten V-TOS), 24 had a supraclavicular scalenectomy (rib

resection; all N-TOS) and 14 had a combined procedure (five A-TOS, nine N-TOS). Eleven were reoperations. Early results (6 months) were available for 122 patients.

Operation	Complete relief	Minor symptoms	Major symptoms	No improvement
First rib resection	45 (50)	23 (25)	8 (9)	4 (4)
Supraclavicular scalenectomy	22 (52)	9 (21)	5 (12)	6 (14)

Overall 91 per cent of patients with A-TOS rated the outcome as excellent/good, compared with 72 per cent of those with N-TOS and nine of ten with V-TOS. Life-table analysis confirmed a durable outcome at up to 6 years. Of 30 patients with A-TOS for whom data were complete, postoperative duplex imaging was normal in 28.

Conclusion: Careful patient selection following a concerted effort at conservative management yields good results. These data are useful for counselling patients who may be facing surgery for this disabling condition.

Clinical governance and the vascular surgeon

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Background: Monitoring of surgeons and their results is currently in question. The validity and the practicality of audit to determine substandard results is undetermined. To test the instrument of audit, statistical modelling was applied to two indicator vascular procedures, elective abdominal aortic aneurysm (AAA) repair and carotid endarterectomy (CEA), with accepted adverse event rates.

Methods: Binomial statistical models for varying adverse event rates were constructed. A power calculation was used in an attempt to predict the case numbers required to determine substandard results for individual surgeons and vascular units. Statistical conventions of power (80 per cent) and upper criterion of rarity (0.05) were used. Previous activity rates for CEA and elective AAA repair were used to predict the time taken to gather these data.

	Alternative rate (%)			
	6	9	12	24
Base rate 6				
No. of adverse events		37	13	4
No. of operations		463	130	21
Study time for unit (years)		4–8	1.9–2.2	0.4–0.3
Study time for individual (years)		12–78	6–22	3.6–0.5
Base rate 3				
No. of adverse events	14	6	4	
No. of operations	281	86	44	
Study time for unit (years)	4–6	1.5–1.2	0.6–0.7	
Study time for individual (years)	15–47	2–14	1–7.5	

Results: Base rates of 3 and 6 per cent were considered, along with a range of alternate practice. Number of adverse events, number of operations to be studied and the time that this would take are shown in the *Table*.

Conclusion: Statistical modelling demands assumptions about accepted adverse event rates, confidence criteria and what constitutes substandard results. Large numbers of patient data are required even for common operations with accepted adverse event rates. These data raise serious questions as to the feasibility of performing clinical governance on the basis of crude morbidity and mortality event rates alone.

Upper limb arterial injuries: experience of 713 patients and analysis of risk factors associated with limb loss

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Background: Experience of upper limb arterial injury management was analysed and risk factors associated with limb loss were identified.

Methods: Between 1987 and 1997, data on 713 patients with 760 upper limb arterial injuries were analysed retrospectively.

Results: The mechanism of injury was stabbing in 52 per cent, gunshot in 23 per cent, blunt trauma in 14 per cent and shotgun in 5 per cent. The most frequently injured vessel was the brachial artery (53 per cent) followed by the axillary (20 per cent), subclavian (14 per cent), radial (7 per cent) and ulnar (6 per cent) arteries. Associated injuries included bony injury in 12 per cent, nerve injury in 39 per cent and remote injury affecting the head, chest or abdomen in 3 per cent. Surgical revascularization was carried out in 95 per cent of patients and arm fasciotomy was necessary in 9 per cent. The limb salvage rate for this series was 96 per cent (27 amputations) and the survival rate was 98 per cent (11 deaths). On stepwise logistic regression analysis, significant ($P < 0.01$) independent risk factors for amputation were blocked graft (odds ratio (OR) 7.6), tense compartment at presentation (OR 6.5), neurological deficit at presentation (OR 5.4) and associated compound fracture (OR 5.4).

Conclusion: Despite good collateral circulation, upper limb arterial injuries carry a considerable risk of limb loss, particularly when associated with soft tissue damage.

Natural history of atherosclerotic renal artery stenosis

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Background: Atherosclerotic renal artery stenosis (ARAS) may result in hypertension and progressive renal failure culminating in dialysis. However, the natural history of ARAS is unclear, and the necessity and timing of intervention is not established. The effect of ARAS on renal function and the control of blood pressure has been investigated.

Methods: Forty-eight patients (median age 73 years) with haemodynamically significant stenosis (more than 50 per cent diameter narrowing) of one or both renal arteries were enrolled in a multicentre prospective study. The patients were divided into three groups: 50–69 per cent unilateral stenosis ($n = 17$; group 1), 70–99 per cent unilateral stenosis ($n = 16$; group 2) and bilateral disease ($n = 15$; group 3). Baseline measurements of serum creatinine, kidney length and diastolic blood pressure were recorded and these were repeated at every 6 months. Any intervention to revascularize the kidney was recorded. Follow-up was for at least 2 years.

Results: Results at 2 years are shown.

	Group 1	Group 2	Group 3
Mortality rate (%)	35	50	43
Intervention	0	0	11
Creatinine ($\mu\text{mol l}^{-1}$)*			
Baseline	98 (87–144)	113 (105–117)	140 (122–242)
Follow-up	104 (86–122)	118 (103–133)	189 (148–275)†
Dialysis	0	0	1
Blood pressure (mmHg)*			
Baseline	83 (76–95)	89 (79–94)	90 (76–100)
Follow-up	85 (70–90)	80 (67–97)	80 (76–98)

*Values are median (interquartile range). † $P < 0.05$ versus baseline (Wilcoxon signed rank test)

The mortality rate in all groups was significant. All patients in group 1 and 2 were managed conservatively whereas the majority with bilateral disease underwent angioplasty ($n = 8$) or surgery ($n = 3$). Despite intervention one patient became dialysis dependent and the creatinine level deteriorated in the remaining patients. In patients with unilateral disease there was no significant change in renal function or blood pressure. Furthermore, renal size (baseline: 102 (96–107) mm; follow-up 100 (96–108) mm) and the number of antihypertensive drugs per patient remained similar.

Conclusion: In patients with unilateral stenosis the effect on renal function and blood pressure seems to be benign and intervention is seldom indicated. Revascularization in patients with bilateral disease does not improve the dismal mortality rate and whether it reduces the requirement for haemodialysis remains unproven.

Effect of chronic renal failure on postoperative mortality rate following arterial reconstruction

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Background: Chronic renal failure (CRF) is both a risk factor for, and a consequence of, peripheral arterial disease. There is also increasing evidence that patients with CRF have a higher mortality rate following arterial reconstruction, but it is not

known whether this is different for aneurysmal or occlusive disease.

Methods: Over 8 years 1718 consecutive arterial reconstructions performed under the care of one consultant were studied prospectively. Patients were defined as having CRF if at the time of surgery the serum creatinine measured more than $400 \mu\text{mol l}^{-1}$, they were undergoing dialysis or they had received a renal transplant. The in-hospital postoperative mortality rate was compared between patients with and without CRF and analysed according to the urgency as well as the type of arterial reconstruction.

Results:

	CRF		No CRF		P
	No.	Deaths	No.	Deaths	
Elective	51	9 (18)	1103	43 (3.9)	<0.01
Urgent/emergency	18	7 (39)	546	77 (14.1)	<0.01
Thoracic/aortic aneurysm	35	8 (23)	391	54 (13.8)	n.s.
Infrainguinal bypass	14	5 (36)	387	25 (6.5)	<0.01

Values in parentheses are percentages. n.s., Not significant

Sixty-nine patients (4 per cent) undergoing arterial reconstruction over the study period were defined as having CRF. Sixteen (23 per cent) of these died following surgery (myocardial infarct seven, multiple organ failure three, stroke one, mesenteric thrombosis one, paraplegia one, respiratory failure one, pneumonia one, failure to thrive one), in comparison to 120 (7.3 per cent) of 1649 patients without CRF. The mortality rate in patients with CRF was highest in those who underwent urgent/emergency surgery and those who had reconstruction for occlusive disease.

Conclusion: Patients with CRF have a threefold increase in mortality rate following arterial reconstruction. Patients undergoing infrainguinal bypass are at particular risk and should be carefully selected and counselled.

Prospective multicentre study of acute renal failure in arterial surgical patients

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Background: Acute renal failure following vascular surgery is associated with a high risk of death. The aims of this study were to identify the incidence and risk factors for acute renal failure in arterial surgical patients.

Methods: A prospective longitudinal clinical study of consecutive arterial surgical patients, including those undergoing interventional radiological procedures, in 13 UK vascular units was devised. Data were collected locally in each unit using a standard pro forma. Impaired renal function was defined as an admission creatinine level greater than $125 \mu\text{mol l}^{-1}$, while a 50 per cent rise in creatinine was defined as acute renal failure.

Results: Some 1566 patients were enrolled by the 13 units in a 6-month interval (January to June 1999); 124 (7.9 per cent) developed postoperative renal failure. The incidence of renal failure varied according to operation type: abdominal aortic aneurysm 17.6 per cent, thoracoabdominal aneurysm 45.4 per cent, carotid endarterectomy 0.8 per cent, aortobifemoral bypass 10.9 per cent, infrainguinal bypass 5.2 per cent, extra-anatomic bypass 5.2 per cent, embolectomy 14.0 per cent, endovascular procedure 5.0 per cent, radiological procedure 4.2 per cent and amputation 4.5 per cent. The in-hospital mortality rate for all patients was 7.2 per cent, which increased to 37.1 per cent in patients who developed acute renal failure. Significant risk factors for the development of renal failure were thoracoabdominal aneurysm repair (45.4 per cent), emergency surgery (19.4 per cent), surgery on the abdominal aorta (17.6 per cent), pre-existing renal impairment (19.4 per cent) and hypertension (8.3 per cent). Diabetes mellitus, hyperlipidaemia, recent angiography, non-steroidal analgesics, metformin or angiotensin converting enzyme inhibitors were not predictive of the development of renal failure. In 21.8 per cent of patients renal failure developed in association with multiple organ failure. No patient who survived developed end-stage renal failure.

Conclusion: The incidence of acute renal failure following arterial surgery was 7.9 per cent associated, as expected, with a significant mortality rate (37.1 per cent). Emergency aortic surgery carried the highest risk. Patients developing acute renal failure required intensive management, including renal support, but no patient survived to develop end-stage renal failure.

Randomized prospective study comparing pre-emptive epidural and intraoperative perineural analgesia for the prevention of postoperative stump and phantom limb pain following major amputation

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Background: The reported incidence of phantom limb pain (PLP) following amputation is up to 85 per cent. This study was designed to compare the efficacy of two perioperative analgesic techniques with respect to postoperative stump pain (POSP) and PLP.

Methods: Patients were randomized prospectively. Group 1 received a pre-emptive epidural for a minimum of 24 h before surgery which was continued after operation. Group 2 had intraoperative placement of a perineural catheter for the administration of local anaesthetic by infusion after operation. All amputations were performed under general anaesthesia. POSP was assessed by visual analogue score (VAS), ranging from 0 to 10. The presence of PLP was assessed 6 and 12 months after operation.

Results: A total of 30 patients were recruited, 12 men and 18 women, of median age 74 (range 47–93) years. Each group was

well matched for concurrent cardiovascular disease and the level of amputation. VAS at 6 h, 1, 2 and 3 days after operation was significantly less in group 1 than group 2 ($P < 0.05$, two-sample t test). Six patients died in each group and one was lost to follow-up. The overall incidence of PLP was 75 per cent at 6 months and 44 per cent at 12 months, with no significant difference between the two groups.

Conclusion: In this series, pre-emptive epidural analgesia significantly reduced the severity of POSP. The incidence of PLP remains disappointingly high regardless of the analgesic technique used.

Impact of a lifestyle clinic on vascular workload: analysis of factors predicting a successful outcome

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Background: Regular exercise and risk factor control has been shown to treat patients with intermittent claudication effectively; however, patients are often non-compliant and never achieve the full benefits of a conservative approach. In this vascular unit, a nurse-led lifestyle intervention clinic has been established with the aim of optimizing the conservative management of such patients. The aim of this study was to assess the short-term impact of this strategy on radiological and operative vascular workload since its introduction in 1997, and to identify factors predictive of a successful conservative outcome.

Methods: The number of operative and radiological lower limb interventional procedures performed between January 1996 and January 1999 was obtained from departmental databases. The details of 145 consecutive referrals to the claudication clinic were also retrieved. These details were entered into a separate database for analysis. The factors analysed included age, sex, duration of symptoms, ankle brachial pressure index and maximal walking distance at the start of the programme, co-morbid problems, smoking history and attendance. The outcome was change in claudication distance after 3 months of therapy. Analysis was performed using logistic and multiple linear regression models.

Results: Open revascularization procedures reduced from 104 in 1996 to 52 in 1998, femoral-to-popliteal bypass procedures reduced from 66 to 18. Iliac and lower limb angioplasties reduced from 133 to 101, and there were 53 major lower limb amputations in 1996 compared with 58 in 1998. The lifestyle clinic achieved a 36 per cent smoking cessation rate. Change in claudication distance ranged from -51 to 3100 (median 126) per cent. None of the factors analysed could significantly predict a successful outcome.

Conclusion: Lifestyle management is an effective strategy in management of claudicants. It can also reduce interventional vascular workload. The prediction of a successful outcome in individual patients may not be possible.

Modelling the effects of the reorganization of vascular services

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Background: Vascular services are currently in a state of evolution in many areas. A study has been carried out to model the economic and outcome implications of possible reconfiguration of vascular services.

Methods: Computer modelling was carried out based on an urban area with a teaching hospital (TH) and four surrounding district hospitals (DGHs) serving a population of 1.8 million. Data for the model were derived from a number of sources including local activity analysis, record linkage for cross-boundary flows, local audit, prospective surveys and systematic literature reviews.

Results: Analysis demonstrated a number of key differences in service provision between the TH and DGHs which were consistent with findings from literature reviews. These included differences in the use of endovascular treatments and femorodistal bypass, differences in case-mix and rates of particular procedures, and differences in outcome as measured by mortality and amputation rates. Computer modelling examined a number of options for the reconfiguration of services, including variations on fully centralized and hub and spoke arrangements. Cost estimates suggested that centralization and hub and spoke would result in an increased cost of £1 240 000–1 430 000 per year for the entire service, with over 80 per cent of these costs being related to expected increases in activity. Consideration of a number of key areas suggested that the resultant changes would save approximately 20 lives, 65 amputations and seven strokes per year for the population under consideration.

Conclusion: Reconfiguration of vascular services is likely to be highly cost effective. There is little difference in expected cost and outcomes between fully centralized and hub and spoke arrangements but the latter is preferred on the basis of decreased shift of resources and strong patient preference for local services.

Prevalence of popliteal aneurysm in patients with abdominal aortic aneurysm or intermittent claudication

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Background: The prevalence of abdominal aortic aneurysm (AAA) in defined risk groups has been well established but the prevalence of popliteal artery aneurysm is unknown. The aim was to discover the prevalence of popliteal artery aneurysm in patients with known AAA and in patients attending a vascular clinic with intermittent claudication (IC).

Methods: The maximum anterior posterior diameter of the popliteal artery was measured by duplex sonography in 200 patients with known AAA attending an established surveillance programme and 325 patients with IC but no aortic aneurysm attending a vascular clinic. In all patients sex, age and height were recorded.

Results:

	AAA (n=200)	IC (n=325)	P
Men*	163 (81.5)	207 (63.7)	0.002‡
Popliteal aneurysm (> 2 cm)*	4 (2.0)	2 (0.6)	n.s.‡
Age (years)†	73(1)	67(1)	<0.0001§
Height (m)†	1.73(0.01)	1.68(0.01)	0.007§
Diameter of non-aneurysmal popliteal arteries (cm)†	0.79(0.01)	0.67(0.01)	<0.0001§

Values in parentheses are percentages; †values are mean(s.e.). N.s., not significant. ‡ χ^2 test, §unpaired *t* test

Conclusion: The prevalence of popliteal aneurysm is 2.0 (confidence interval 0–3.9) per cent in patients with AAA and 0.6 (0.2–1.4) per cent in patients with IC. Compared with claudicants, patients with AAA are significantly older and taller, more likely to be men and have larger popliteal arteries. The prevalence of popliteal aneurysm is too low, even in suspected high-risk groups, for screening to be worthwhile.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Experience with the preperitoneal 'plug and patch' inguinal hernia repair

Sir

We read with interest the short note by Goyal *et al.* (*Br J Surg* 1999; 86: 1284–5) and entirely agree with the concept of tension-free inguinal hernia repair. We congratulate the authors on their large series and would appreciate clarification of two operative steps. First, regarding dissecting and inverting the indirect sac, we assume that all these indirect hernias had small incomplete sacs as complete scrotal sacs (congenital preformed sacs) would not be suitable for this approach. Second, we do not understand the need for 'plug and patch' in all patients. The patch is a modification of Lichtenstein's technique and is more than sufficient to prevent recurrence of both direct and indirect hernias. We are sure the plug has a role for a recurrent hernia where the mesh-plug can be fixed to the rim of scar tissue as originally described by Robbins and Rutkow¹. We use the standard polypropylene mesh which is manually shaped and consider the routine use of a plug unnecessary in terms of cost and steps in the operative technique.

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1 Robbins AW, Rutkow IM. The mesh-plug hernioplasty. *Surg Clin North Am* 1993; 73: 501–12

Authors' reply

Sir

We thank Ramanand *et al.* for their interest in our article. The majority of indirect hernias repaired by this approach were confined to the inguinal canal but some descended to the scrotum. The inguinoscrotal sacs take longer to separate from the cord but can be managed in the same fashion and on occasion the sac is divided at the neck of the scrotum. To date, we have not encountered an indirect sac which cannot be managed in this way including those associated with incarcerated and sliding hernias.

In the UK there is little emphasis on the cost of time spent in the 'operating room' but this is not the case in the USA and other countries. While the cost of this approach for biomaterials used (plug and patch *versus* mesh alone) are higher, the overall cost is lower as the repair takes less time to perform¹.

We too were rather sceptical of the benefits of this type of repair but our results and patients' comments and the paucity of complaint about postoperative pain have only encouraged us to continue with its use. Since we have had no recurrences of the 170 indirect hernias to date we have contemplated avoiding the on-lay patch altogether. However, as the canal is open why not place a patch to strengthen the posterior wall and help prevent future direct herniation. As Kingsnorth *et al.*¹ recently stated 'the approach is hypnotically simple' and, more importantly, it works.

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1 Kingsnorth AN, Bennett D, Walker A, Porter C. Randomized double-blind study to compare the short-term outcome of the Lichtenstein operation with the Perfix plug in inguinal hernioplasty. *Br J Surg* 1999; 86 (Suppl. 1): 20 (Abstract).

Consultant surgeons' opinion of the skills required of basic surgical trainees

Sir

Baldwin *et al.* (*Br J Surg* 1999; 86: 1078–82) reflect on consultant surgeons' views of the skills required by basic surgical trainees. I note that this paper was accepted in March 1999 and I would be interested to know the period of data collection. I wonder whether the recent interest in 'skills associated with clinical governance' referred to in the Discussion, and which the 111 consultant surgeons did not consider important, reached a crescendo some time after the conduct of this survey. If that is the case, then it would be of interest to ascertain the views of colleagues now.

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Authors' reply

Sir

We thank Professor Spigelman for his interest in our paper. The questionnaire survey was carried out at the end of 1997, shortly after the concept of clinical governance was introduced into the National Health Service in the UK. Corporate governance, aimed at redressing failed standards in the business world, was first described in 1992¹ and the concept was adapted

for use within the clinical environment following a government White Paper in 1997². It may well be that clinical governance was not considered important by consultants as it had not reached its high level of acceptance at the time of the survey.

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- 1 *Report of the Committee on the Financial Aspects of Corporate Governance* London: Gee, 1992.
- 2 Secretary of State for Health. *The new NHS* London: Stationary Office, 1997 (Cm 3807).

Postoperative peritonitis originating from the duodenum: operative management by intubation and continuous intraluminal irrigation

Sir

I read with interest the technique described by Parc *et al.* (*Br J Surg* 1999; 86: 1207–12) but have one or two questions. Were any specific inclusion criteria, such as the duration or size of fistula, patients' albumen or sickness score, used? What previous repair procedures had been undertaken? What were the original operations (postgastrectomy suture-line leaks seem one large group)? What proportion of patients had multiloculated abscesses as opposed to peritonitis? Was there any specific reason to choose a combination-corrugated over a sump drain? Or to change tubes at 21 days? Is a gastrostomy still used as originally described¹? Would more laparostomies ('retroperitoneal laparostomies'²) perhaps have been associated with fewer wound complications compared with attempts at closure with polyglactin mesh or relaxing incisions?

The original logic¹, that intubation or suture closure are the only two options where a stoma is not feasible, perhaps ignores drainage and decompression with or without reinforced repair (using omentum or jejunum). Tubes may fall out, especially during irrigation regimens. Purse-string sutures at the fistula site, like anastomoses, frequently give way. A second assumption, that irrigation and dilution are vitally important for the healing of such fistulas, would have been clearly proven if compared with a suitable control group. The use of contemporaneous well matched, rather than historical, controls would also have excluded the confounding influence of octreotide along with better nutritional support and interventional radiology.

Techniques such as duodenal diverticulization³, pyloric exclusion⁴ or even decompressing tube duodenostomies, although developed primarily for duodenal trauma, are very useful in such situations. The technique of intubation and irrigation, although promising, needs to be studied further before advocating it as a possible second-line procedure where more standard techniques fail.

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- 1 Levy E, Cugnenc PH, Frileux P, Hanoun L, Parc R, Huguet C *et al.* Postoperative peritonitis due to gastric and duodenal fistulas. Operative management by continuous intraluminal infusion and aspiration: report of 23 cases *Br J Surg* 1984; 119: 659–63
- 2 Fang JF, Chen RJ, Lin BC, Hsu YB, Kao JL, Kao YC *et al.* Retroperitoneal laparostomy: an effective treatment of extensive intractable retroperitoneal abscess after blunt duodenal trauma. *J Trauma* 1999; 46: 652–5
- 3 Berne CJ, Donovan AJ, White AJ, Yelli AE. Duodenal 'diverticulization' for duodenal and pancreatic injury. *Am J Surg* 1974; 127: 503.
- 4 Vaughan GD, Frazier OH, Graham DY, Mattox KL, Petrecky FF, Jordan GL. The use of pyloric exclusion in the management of severe duodenal injuries. *Am J Surg* 1977; 134: 785.

Authors' reply

Sir

We read with interest the letter from Mr Sharma which raises several points.

Inclusion criteria – duodenocutaneous fistulas and abscesses were excluded from the study, retaining only patients with extensive postoperative peritonitis. All patients were critically ill with a mean Acute Physiology and Chronic Health Evaluation II score of 17.7.

Previous repair – thirty-one patients (63 per cent) had been referred after a failed attempt at controlling the duodenal leak. The procedure was either an intubation alone or a suture of the defect.

The original operations were the following: Billroth I gastrectomy (five), Billroth II gastrectomy (12), suture of perforated ulcer (12), cholecystectomy (six), choledochoduodenostomy (two), miscellaneous (11).

Drains and tubes – the combination of tube and corrugated drain is the standard drainage method at this hospital and were removed at a mean of 21 days, as soon as the spiral drain collected the majority of the effluent. Gastrostomies are no longer used.

A retroperitoneal laparostomy is not a simple way of treatment. To close the abdomen and control the fistula is more practical in terms of local care and patient comfort. Significant abdominal wall complications have disappeared following the use of the polyglactin mesh.

Duodenal 'decompression' (or rather 'disconnection'), a procedure associating antrectomy, gastrojejunostomy and tube duodenostomy, diverts the duodenum from the digestive circuit but not from biliary and pancreatic fluids. This procedure has given good results in patients with trauma^{1,2} and perforated ulcers^{3,4}, but in those with duodenal fistula the rate of recurrent abscess was 60–100 per cent^{5,6}.

Accidental tube displacement – this threat lead to a design of a spiral-shaped drain that is self-retaining. After a few days, the granulation tissue around the tube takes the shape of an internal groove, preventing removal by simple traction on the drain. In this series spiral drains were not displaced despite restlessness in patients (secondary to sepsis).

Randomized trials are irrelevant in small groups of complex and heterogeneous cases. In this centre we tried several procedures until a dramatic change in mortality rate was detected.

Why irrigation? As mentioned above, the duodenal fluid usually leaks around the tube and the irrigation is to neutralize the fluid before its leakage into the periduodenal area.

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- 1 Berne CJ, Donovan AJ, White EJ, Yelli AE. Duodenal 'diverticulization' for duodenal and pancreatic injury. *Am J Surg* 1974; 127: 503–7.
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Retrosternal goitre

Sir

Professor Wheeler's extensive experience of thyroid surgery is reflected in his advice about removing retrosternal goitres (*Br J Surg* 1999; 86: 1235–6). As he says, median sternotomy is rarely required, but its need may be further reduced by excision of the inner half of the clavicle which improves the exposure¹.

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- 1 Armour RH, Conway M, Shenoy KN. Retrosternal goitre: a wider view. *Br J Surg* 1997; 84: 403.

A 14-year experience with 6 cm as a criterion for surgical treatment of abdominal aortic aneurysm

Sir

I write to support the conclusion of Scott *et al.* (*Br J Surg* 1999; 86: 1317–21) that, with the exceptions they list, patients with asymptomatic abdominal aortic aneurysm less than 6 cm in diameter should not be operated on but should be kept under surveillance. In a prospective post-mortem study of 39 ruptured abdominal aortic aneurysm only two were less than 6 cm in diameter (Table 1).

Table 1

Diameter	Number (M : F)
5.0–5.9	2 : 0
6.0–6.9	2 : 1
7.0–7.9	7 : 2
8.0–8.9	7 : 0
9.0–9.9	5 : 2
10.0–10.9	8 : 0
11.0–11.9	2 : 0
12.0–12.9	0 : 0
13.0–13.9	1 : 0
Total	34 : 5

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Management of liver trauma

Sir

Parks *et al.* (*Br J Surg* 1999; 86: 1121–35) should be congratulated for their thorough review of the management of liver trauma. However, for the general readership of the *BJS* perhaps more emphasis should be made of a number of important issues

First, most patients present with 'abdominal trauma' rather than a liver injury and those having surgery are usually subjected to a 'blind' laparotomy. It is our belief that the majority of patients presenting with blunt abdominal trauma can and should be stabilized sufficiently so that contrast-enhanced computed tomography (CT) of the abdomen may be performed by an experienced radiologist. Many patients ultimately referred to us would have been urgently transferred rather than operated on if the initial operating surgeon had known the extent of the liver injury.

Second, a high proportion of patients with even grade IV and V liver injury can be managed conservatively. The risk of missing associated organ injury on infusion CT is small and so we can see little benefit from either abdominal ultrasonography or diagnostic peritoneal lavage (both recommended in the paper). To ensure a successful outcome, however, patients may require the resources of a specialist multidisciplinary team and repeated examination, monitoring and investigation.

Third, the detailed description of the various methods of dealing with liver trauma during an operation is well written but may encourage non-specialist liver surgeons to attempt over-ambitious operations. It is our belief that the small proportion of patients with liver trauma who cannot be stabilized enough to be transferred direct to a specialist unit should simply have perihepatic packing followed by transfer.

In a series of 43 consecutive patients referred to the Birmingham Liver Unit between 1991 and 1999, 23 were treated conservatively at the referring hospital with an eventual mortality rate of 13 per cent. This compares with a mortality rate of 30 per cent in the 20 patients undergoing surgery at the referring hospital. Although there were differences between the groups, both had a median American Association for the Surgery of Trauma¹ liver injury scale of at least III. The time interval in the latter group from admission to surgery at the referring hospital (in cases for which the information was available) was a mean of 5 h (median 3.5 h), supporting the concept of early imaging being possible in the majority of patients. We strongly support the conclusion of Parks *et al.* that, whenever possible, patients should be transferred to regional hepatobiliary centres.

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- 1 Moore EE, Shackford SR, Pachter HL, McAninch JW, Browner BD, Champion HR *et al.* Organ injury scaling: spleen, liver and kidney. *J Trauma* 1989; 29: 1664–6.

Simultaneous aortic aneurysm repair and colonic surgery

Sir

We read with interest the article by Oshodi *et al.* (*Br J Surg* 1999; 86: 217–18) and thank the authors for raising this controversial topic for discussion. Although no clear consensus is available among professors of vascular and general surgery¹, the authors have concluded that a simultaneous procedure is the preferred way to deal with this difficult problem. Evidence suggests that the majority of surgeons, including ourselves, think otherwise².

The authors draw their conclusions from an experience of nine patients, of whom four had an infarcted colon. It is not clear from the data whether these four patients presented with

simultaneous aortic aneurysm and colonic ischaemia.

Mortality in this group was 50 per cent – an unacceptably high figure in our view. If this group is excluded, the authors are making recommendations based on the experience of only five patients over a 20-year period and it is not clear what investigations were used to exclude graft infection.

Until the management of coexisting aortic aneurysm and colonic pathology is examined systematically by a larger multicentre study, we believe we should perform staged operations and treat the lesion that poses the greater immediate threat to the patient first.

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- 1 Lobbato VJ, Rothenberg RE, La Raja RD, Georgiou J. Coexistence of abdominal aortic aneurysm and carcinoma of the colon: a dilemma. *J Vasc Surg* 1985; 2: 724–6.
2 Morris HL, DaSilva AF. Coexisting abdominal aortic aneurysm and intra-abdominal malignancy. reflections on the order of treatment. *Br J Surg* 1998; 85: 1185–90.

Authors' reply

Sir

Thank you for the opportunity of reply. The four patients with infarction of the colon all had leak or rupture of the aorta at the time of surgery and there was no element of choice in their management. In the circumstances we do not think that most surgeons would consider a mortality rate of 50 per cent (in patients aged 76, 77, 78, 79 and 80 years) 'unacceptably high'. All patients were monitored for evidence of graft failure or infection until death, usually from unrelated causes. Those who died immediately after operation had post-mortem examination but it was obviously too early to dismiss graft infection as a potential problem if they had left hospital.

We agree that the risk of graft infection makes most surgeons think that staged operation would be the best policy, but the significant high rate of interval rupture makes it difficult to determine which lesion should be treated first¹, particularly in patients with cancer. The double procedure carries increased risks and greatly extends the periods as a patient for those with a short life expectancy (four of our patients died within 5 years). The benefits of a single procedure may therefore easily outweigh the risk of graft infection.

We agree that a systematic multicentre study is needed and suggest a multicentre register of these patients in the first instance (which we hope to establish) as other types of study may be difficult to sustain because of the rarity and complexity of these dilemmas when they arise.

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A hernia sac cannot be found at operation

Letter 1

Sir

I was surprised that no mention was made in this article (*Br J Surg* 1999; 86: 1107) of how to prevent or simplify the problem. As a young surgeon at St Mary's Hospital, London I was taught that when a patient came into the anaesthetic room he or she should be examined and the hernial bulge accurately circled with a marking pen. This may involve standing the patient up and asking them to cough vigorously or even to jump up and down! If no bulge is definable the patient should be returned to the ward for later review.

At operation a keen eye should be kept on the marked site and if no hernia sac is found that site should be explored for other pathology, i.e. lymph nodes, lipoma, cyst, etc. If nothing definite is found I think a judgement has to be made depending on how sure the surgeon was that there was an abnormality and on the patient's symptoms. I think a good case could be made for closing the wound and reviewing the patient at a later date.

The importance of taking a good history and carrying out a thorough preoperative examination by the operating surgeon cannot be overemphasized. A considered and orderly withdrawal is often not only the safest line of action but the most sensible.

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Letter 2

Sir

The article by Waters offers sensible advice when a hernia sac cannot be found at open surgery. I have recently encountered a similar situation during laparoscopic surgery. A 50-year-old Caucasian man, weighing 108 kg, presented with bilateral intermittent groin swellings with definite cough impulses and, after appropriate counselling, he agreed to laparoscopic preperitoneal bilateral inguinal hernia repair. Laparoscopy revealed completely normal anatomy in both groins. All hernial orifices were clearly identified and no peritoneal sacs were present. Because of the patient's obesity it was presumed that

the cough impulses were the bulges of Morgagni and no procedure was performed. At subsequent review he continued to complain of discomfort in the groins with intermittent bulges and cough impulses; a further laparoscopy was arranged. Again no evidence of any hernia sac was found and again no repair was performed. Following this, the patient continued to complain of symptoms very suggestive of a hernia and an open exploration was performed on the more symptomatic groin. A large lipoma of the cord representing an indirect hernia without hernia sac was found and conventional mesh repair carried out, following which he was symptomatically better.

At open repair, if no hernia sac is found in an adult patient, posterior wall repair is performed routinely. The situation is, of course, different at laparoscopy since the anatomy can be inspected without dividing the external oblique and cremaster and therefore the groin is not weakened. However, the presence of an extraperitoneal hernia cannot be excluded without undertaking a dissection and the advice should probably be to go ahead and perform mesh repair whatever the laparoscopic findings.

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Letter 3

Sir

We read this clinical dilemma with interest and feel that this problem may occur more frequently than realized. During preperitoneal laparoscopic mesh repair the dynamic relationship between the cord, the peritoneum (sac) and the deep inguinal ring can be observed during the creation of the preperitoneal space. Of 25 preperitoneal hernia repairs at this institution, two patients had a lipoma of the cord and the absence of a peritoneal sac extending into the deep ring confirmed the diagnosis.

The presence of a spermatic cord lipoma is not an uncommon finding during inguinal hernia repair¹. Previously, it has been regarded as an incidental accompaniment to the hernia sac. At open surgery, when traction is applied to the spermatic cord to demonstrate the sac, a piece of normally placed peritoneum may be pulled into the deep ring creating an artificial 'small hernia sac' which may be resected. During laparoscopic preperitoneal repair the lack of a sac can be clearly seen and the lipoma more easily identified for what it is.

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- 1 Ponka JL. *Hernias of the Abdominal Wall*. Philadelphia, Pennsylvania. W.B. Saunders, 1980.
- 2 Truong S, Pfingsten FP, Dreuw B, Schumpelick V. Stellenwert der sonographie in der Diagnostik von unklaren Befunden der Bauchwand und Leistenregion. *Chirurg* 1993; 64: 468–75.

Authors' reply

Sir

The article was, of necessity, restricted to the particular 'clinical dilemma' of a sac not being found at operation. The history and examination are both important. On rare occasions I have found a hernia at operation when I have been convinced by the patient's history but have been unable to feel it. Skin marking might be useful in the young and thin but in we older and stouter the mobility of the skin surface may give little clue to the position of deeper structures.

The respective letters from Newcastle and Dublin rightly emphasize that lipomata of the cord are true hernias originating extraperitoneally and travelling through the deep ring. Although they may encircle a peritoneal sac, they also appear as 'sliding lipomata', i.e. peritoneal-less inguinal hernias, often symptomatic and not seen transabdominally.

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Expression and clinical significance of apolipoprotein D in male breast cancer and gynaeomastia

Sir

The study by Serra *et al.* (*Br J Surg* 1999; 86: 1190–7) does not mention the criteria used for selecting the treatment modality in the patients with breast cancer. Sixty-five patients in this study had invasive breast carcinoma treated with a radical or modified radical mastectomy; only 34 received locoregional radiotherapy. It is recognized that radiotherapy reduces locoregional recurrence in patients with breast carcinoma^{1,2}. Locoregional radiotherapy in combination with chemotherapy may prolong survival compared with chemotherapy alone³. Treatment difference was not included in the statistical analysis and it is therefore not possible to attribute the observed difference in locoregional recurrence and survival to the expression of apolipoprotein D.

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- 1 The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Canadian Association of Radiation Oncologists. Breast radiotherapy after breast-conserving surgery. *Canadian Medical Association Journal* 1998; 158 (Suppl. 3): S35–42.
- 2 Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE *et al.* Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997; 337: 956–62.
- 3 Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F *et al.* Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b trial. *N Engl J Med* 1997; 337: 949–55.

Authors' reply

Sir

Patients with male breast cancer who were included in our study were diagnosed and treated between 1979 and 1995. This was a multicentre study with 17 participating centres and patients were treated using different criteria for the selection of modalities. Analysis of the impact of radiotherapy or chemotherapy was not the aim of the study.

Criteria used for selecting adjuvant treatment are normally based on tumour size and node status. Apolipoprotein D HSCORE levels in our patients were significantly correlated with axillary node involvement, a major criteria for the use of radiotherapy and/or chemotherapy. Radiotherapy and chemotherapy were not included in the multivariate analysis to avoid unnecessary covariables in the study. We have, however, analysed both factors and neither was associated with shorter relapse-free or overall survival periods.

The results of our study suggest that apolipoprotein D may be a new prognostic factor in breast cancer of both sexes and further studies of this androgen-induced protein and other prognostic factors will be undertaken.

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Randomized clinical trial of early laparoscopy in the management of acute non-specific abdominal pain

Sir

I read with interest the article on early laparoscopy in the investigation of patients with non-specific abdominal pain (NSAP) by Decadt *et al.* (*Br J Surg* 1999; 86: 1383–6). As NSAP is the commonest reason for surgical admission it is surprising that only 146 patients were recruited over a 3-year period. If patients underwent laparoscopy within 18 h of admission how can the median (range) time to surgery be 10 (2–39) hours?

Evidence to support the conclusion that the use of laparoscopy *per se* improved patient's quality of life is tenuous.

A similar improvement in patient well-being scores was seen within both groups but no direct comparison between the groups was presented. The placebo effects of medical interventions are well recognized. Data regarding improvement in quality of life in those eventually undergoing surgery from the observation group would have been interesting. As over 70 per cent of patients in the observation group avoided surgery without increased morbidity, hospital stay or readmission, an alternative interpretation of the data is that 'active observation' is a safe practice¹. Laparoscopy used to provide the patient with a diagnosis is unnecessary, particularly when intraoperative recognition of acute appendicitis is unreliable² and a histological diagnosis is only obtained after the patient has been discharged from hospital.

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- 1 Thompson HJ, Jones PF. Active observation in acute abdominal pain. *Am J Surg* 1986; 152: 522–5.
- 2 Grunewald B, Keating J. Should the 'normal' appendix be removed at operation for appendicitis? *J R Coll Surg Edinb* 1993; 38: 158–60

Letter 2

Sir

We congratulate Decadt *et al.* on their randomized controlled trial of early laparoscopy in the management of patients with NSAP but question the role of ultrasonography in their study.

Patients with NSAP were randomized to early laparoscopy or observation after baseline investigations had been performed. Ultrasonography was not a baseline investigation. Of 59 patients randomized to early laparoscopy, four (6.8 per cent) had ultrasonography but it is not clear why. Of 61 patients randomized to the observation group, only 34 (55.7 per cent) had ultrasonography, but the criteria for the decision to perform a scan were not given.

Ultrasonography might have been used to better effect as it has been shown that it is useful in establishing a diagnosis in these patients¹ and increases the diagnostic accuracy in patients with suspected acute appendicitis². All patients could have been scanned before randomization and those with obvious pathology excluded (probably the most ethical design), or all patients randomized into the observation group should have been scanned as part of a 'watch and wait' policy. Controlling the use of ultrasonography would have given the results greater impact.

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- 1 Gaensier EHL, Jeffrey RB Jr, Laing FC, Townsend RR. Sonography in patients with suspected acute appendicitis: value in establishing alternative diagnosis. *AJR Am J Roentgenol* 1989; 152: 49–51.
- 2 Galindo Gallego M, Fadrique B, Nieto MA, Calleja S, Fernández-Aceñero Ais G *et al.* Evaluation of ultrasonography and clinical diagnostic scoring in suspected appendicitis. *Br J Surg* 1998; 83: 37–40.

Letter 3

Sir

Studies in the 1960s showed that about one-third of patients admitted with acute abdominal pain recovered without treatment within 24–48 h and are considered to have acute NSAP^{1,2}. Active observation (AO) was introduced to identify this group and has proved to be a safe and reliable way of reducing unnecessary appendicectomy rates from 20 to 30 per cent to below 10 per cent^{3,4}.

Decadt *et al.* placed all patients who did not proceed to operation in the NASP category and concluded that their management can be improved by proceeding to laparoscopy. This increased diagnostic return. The question must be asked whether, knowing that one-third will settle under AO, it is wise to laparoscope the whole group. This policy was followed by significant complications and one postoperative death.

Patients who prove to have NSAP quickly show steady improvement. It seems contrary to the interests of these patients and hospital finances not to allow time for this diagnosis to declare itself. Attention would then be concentrated on the remaining patients for some of whom laparoscopy will be indicated.

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- 1 Jones PF. Acute abdominal pain in childhood with special reference to cases not due to acute appendicitis. *BMJ* 1969; 1: 284–6.
- 2 DeDombal FT, Leaper DJ, Staniland JR, McCann AP, Horrocks JC. Computer-aided diagnosis of acute abdominal pain. *BMJ* 1972; 2: 9–13
- 3 Dolgin SE, Beck AR, Tartter PI. The risk of perforation when children with possible appendicitis are observed in hospital. *Surg Gynecol Obstet* 1992; 175: 320–4
- 4 Jones PF, Bagley FH. Acute appendicitis. In Jones PF, Krukowski ZH, Youngson GG (eds). *Emergency Abdominal Surgery* (3rd ed) London: Chapman & Hall, 1998: 49–52.

Author's reply*Sir*

We thank Mr Parker for his interest in our paper. The number of patients recruited over the 3-year study period is explained by the strict entry criteria and the fact that patients were recruited only when the team represented by the authors was on call.

The strength and longevity of the placebo effect is important and long-term studies are underway to assess this as well as collection of long-term data regarding readmission.

Messrs Kerwat and Hardwick make helpful comments. Our study was designed primarily to assess the role of laparoscopy. The use of ultrasonography within a few hours of admission was reserved for patients where an ectopic pregnancy was suspected. It was also used in one patient suspected of having gallstones but in whom none was found. In the group of patients randomized to observation and investigation, ultrasonography was far more widely utilized, in line with the indications mentioned by the Cardiff team. It might have been

better to avoid ultrasonography altogether in the patients randomized to early laparoscopy, but four did undergo the procedure before laparoscopy.

We thank the group from Aberdeen for their comments. We accept that there was morbidity from early laparoscopy (after a laparotomy it might be added) but there was also morbidity and indeed mortality in the active observation group. It seems that whichever method of treatment is used there will be some morbidity and mortality in patients admitted with acute NSAP. Whether the advantages seen in patient satisfaction and diagnostic rate are enough to advocate early laparoscopy in all patients is uncertain. We intend to study readmission and well-being in these two cohorts to determine whether there are other advantages to early laparoscopy.

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Trauma. A Companion to Bailey and Love's Short Practice of Surgery

D. V. Skinner and F. Whimster (eds)

277 x 217 mm Pp 354. Illustrated 1998 London: Arnold £95

This book is a review, sometimes in somewhat dogmatic style, of recent views about the management of major trauma. The preface declares that its target audience is students, trainees and consultants. There is no doubt that this is a comprehensive and authoritative collection of chapters. The emphasis is mainly on civilian, as opposed to military, trauma, and the tone of the book is aimed more at European trauma than the predominant knife and gunshot wounds of the USA and South Africa, although these too are comprehensively covered. I have several quibbles. Some of the statements in the volume might be challenged. For example, 'a plain chest X-ray would exclude major thoracic problems that have not been diagnosed clinically' and 'upper gastrointestinal endoscopy may be helpful if injury is suspected to the lower oesophagus or duodenum'. Some of the thinking on the management of major abdominal trauma is out of date. Diagnostic peritoneal lavage is said to be used increasingly, whereas with the advent of new spiral computed tomography, even for an unstable patient, its use is becoming less. The management of liver trauma is disappointing. The emphasis on packing could be greater, and little mention is made of diagnostic and therapeutic arteriography as an adjunct to controlling severe haemorrhage. The non-operative management of splenic trauma, particularly in children, barely gets a mention, and only 16 pages on the management of orthopaedic trauma of the limbs seems rather scant. The quality of the radiographs is variable. All in all, however, this book will be a useful reference point, particularly for those studying for examinations and formulating their thinking on the organization of trauma units and teams.

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The Evidence for Vascular Surgery

J. J. Earnshaw and J. A. Murie (eds)

302 x 213 mm Pp 210 Illustrated 1999 Kamberton TFM Publishing £37 50

This is an unusual text in that it takes topics and looks at the evidence for management. All the main areas in vascular surgery are covered. The overall standard of the chapters is excellent and highlights the salient points well. There is, however, a significant difference to which some of the chapters are referenced, but the idea of highlighting key references in bold is helpful. A criticism is the use of a grey background for the tables and summary points. This background does not make for easy reading and I trust that the editors may change this form of highlighting in future editions. Overall, I think this is an excellent text which will be useful for both trainees and practising consultant vascular surgeons and I look forward to seeing the second edition. Hopefully some of the questions posed by this text will, by then, have been answered.

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Scientific Surgery

Jivonen MK, Koskinen MO, Ikonen TJ, Matikainen MJ. Emptying of the jejunal pouch and Roux-en-Y limb after total gastrectomy – a randomised prospective study. *Eur J Surg* 1999; **165**: 742–7. Forty-nine patients were randomized at original operation. Some 15 months later, 45 were alive and had emptying studies. Jejunal pouch reconstruction was associated with slower upper gut emptying, better eating capacity and fewer postoperative symptoms.

Brown TA, McDonald J, Williard W. A prospective, randomized, double-blinded, placebo-controlled trial of cisapride after colorectal surgery. *Am J Surg* 1999; **177**: 399–401. Treatment with cisapride speeded return of bowel function and reduced hospital stay by a median of 1 day in this trial including 35 patients.

Cina CS, Clase CM, Haynes BR. Refining the indications for carotid endarterectomy in patients with symptomatic carotid stenosis: a systematic review. *J Vasc Surg* 1999; **30**: 606–17. Twenty-three publications were analysed. For stenoses greater than 70 per cent, surgery was accompanied by a relative risk reduction from death or major stroke of 48 per cent. The corresponding figure for stenoses of 50–69 per cent was 27 per cent. In patients with a lesser stenosis surgery was 'harmful'.

Preclik G, Grune S, Leser HG, Lebherz J, Hedwein W, Machka K *et al.* Prospective, randomised, double blind trial of prophylaxis with single dose of co-amoxiclav before percutaneous endoscopic gastrostomy. *BMJ* 1999; **319**: 881–4. Some 106 patients were randomized, prophylaxis reduced the risk of wound and other infective complications – serious infections occurred in 2 per cent of treated patients and 26 per cent of controls ($P < 0.01$).

Hojris I, Overgaard M, Christensen JJ, Overgaard J on behalf of the Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. Morbidity and mortality of ischemic heart disease in high-risk breast cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. *Lancet* 1999; **354**: 1425–30. The result of this long-term study including 3083 women was that radiotherapy reduced the mortality rate at 10 years from breast cancer (44.2 versus 52.5 per cent) but did not increase mortality from ischaemic heart disease (0.8 versus 0.9 per cent respectively).

Jiang ZM, Cao JD, Zhu XG, Zhao WX, Yu JC, Ma EL *et al.* The impact of alanyl-glutamine on clinical safety, nitrogen balance, intestinal permeability and clinical outcome in postoperative patients: a randomised double blind controlled study of 120 patients. *J Ent Parent Nutr* 1999; **5**: Suppl. S62–6. Sixty patients undergoing major abdominal surgery in two centres were studied. Parenteral nutrition supplemented by alanyl-glutamine improved nitrogen balance and reduced hospital stay by a mean of 4 days.

Lillemoe KD, Cameron JL, Haracre JM, Sohn TA, Santer PK, Coleman J *et al.* Is prophylactic gastroenterostomy indicated for unresectable periampullary cancer: a prospective randomised trial. *Ann Surg* 1999; **230**: 322–30.

Eighty-seven patients with pancreatic cancer not at immediate risk of gastric outlet obstruction were randomized. Mean survival was similar but eight of 43 control patients developed gastric outlet obstruction compared with none who had gastroenterostomy.

Picchio M, Lombardi A, Zolovkins A, Mihelsons M, La Torre G. Tension free laparoscopic *versus* open hernia repair: a randomised controlled trial of early results. *World J Surg* 1999; **23**: 1004–9. There were no important differences in recovery time in this trial of 105 patients, but laparoscopic repair was associated with less postoperative pain.

Vaezi MF, Richter JE, Wilcox CM, Schroeder PL, Birgisson S, Slaughter RL *et al.* Botulinum toxin *versus* pneumatic dilatation in the treatment of achalasia: a randomised trial. *Gut* 1999; **44**: 231–9. Pneumatic dilatation was more effective up to 1 year in this study of 42 patients. Dilatation had a higher cumulative remission rate and an improvement in objective parameters.

Uhl W, Buchler MW, Malfertheiner P, Beger HG, Adler G, Gaus W and the German Pancreatitis Study Group. A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut* 1999; **44**: 97–104. Some 302 patients were randomized to one of three groups (two different doses of octreotide and one control). Mortality rates were similar in all three groups and no other advantages for octreotide were detected.

Abu Rhama A, Robinson PA, Holt SM. Prospective controlled study of polytetrafluoroethylene *versus* saphenous vein in claudicant patients with bilateral femoropopliteal bypasses. *Surgery* 1999; **126**: 594–602. Forty-three patients who had bilateral above knee bypasses had vein used on one side and polytetrafluoroethylene on the other. Although there were more perioperative complications with vein (12 versus 5 per cent), patency rates were similar at 72 months, although more vein grafts had needed revision.

Morrow M, Rademaker AW, Bethke KP, Talamouti MS, Dawes LG *et al.* Learning sentinel node biopsy: results of a prospective randomised trial of two techniques. *Surgery* 1999; **126**: 714–22. Ninety-two patients were randomized to blue dye localization alone, or with added radioactivity. Addition of radioactivity did not improve the sentinel node detection rate (86 versus 88 per cent for dye alone).

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This must not exceed 200 words and should be presented in a structured format. **Background:** state why the study was done and its main aim. **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings including important numerical values. **Conclusion:** state the main conclusions but controversial or unexpected observations may be highlighted.

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Use abbreviations *sparingly*. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension.

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For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; 78: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

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Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637–9).

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Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

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Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

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Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript¹ or ^{1–3}. References cited only in tables or figures should be numbered in sequence.

Barrett's oesophagus – 50 years on

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Norman Barrett first described the columnar-lined oesophagus in this journal in 1950¹; he believed it to be associated with a congenital short oesophagus. Fifty years on, we are much clearer about its aetiology, pathophysiology and malignant potential, but controversies remain. It is of particular concern that the incidence of oesophageal adenocarcinoma, as a consequence of gastro-oesophageal reflux disease (GORD) and Barrett's oesophagus², is increasing more rapidly than that of any other malignancy in the Western world. The influence of pharmacological, endoscopic and surgical treatments on this incidence, and the benefits of surveillance programmes, are unknown.

There is now very strong evidence that Barrett's oesophagus is an acquired condition consequent on long-standing GORD. Approximately 10 per cent of patients with GORD will develop Barrett's oesophagus. Intestinal metaplasia is a necessary prerequisite to the development of adenocarcinoma, which now occurs with an incidence of 1–1.5 per cent per annum, equating in the UK to approximately 10 cases per 100 000 population. This represents an eightfold increase in the past three decades, with a consequent increase in the proportion of oesophageal tumours that are adenocarcinomas from less than 10 per cent to over 50 per cent in most centres. Caucasian men who smoke, and those who have long-segment (greater than 7 cm) disease, have intestinal metaplasia of long duration, especially with reflux of duodenal as well as gastric contents, are at greater risk. Malignant transformation occurs in a stepwise process from metaplasia through dysplasia to carcinoma, involving a series of molecular changes that include p53 and p16 mutations, aneuploidy and microsatellite instability³.

Management of Barrett's oesophagus is controversial. In the absence of complications, many authorities advise no treatment unless symptoms are present. However, many patients are asymptomatic due to diminished mucosal sensitivity, and the aims of treatment are more to do with influencing the natural history of the disease rather than symptom relief. Proton pump inhibition may result in the development of squamous islands, but it does not result in regression of the metaplastic segment. Two studies have shown a lesser influence of acid suppression on the natural history of the metaplastic segment, as measured by healing

of coexisting strictures, appearance of new strictures and change in length, than antireflux surgery⁴. This probably relates to the documented difficulty in normalizing oesophageal acid exposure in these patients with high-dose proton pump inhibition therapy⁵, and the finding that such therapy is relatively ineffective in normalizing bile reflux compared with fundoplication⁶.

Antireflux surgery offers the prospect of correcting the underlying pathophysiological defects which militate against the efficacy of acid suppression therapy, particularly lower oesophageal sphincter failure, duodenogastro-oesophageal reflux and hiatal hernia, which are present in the majority of patients with Barrett's oesophagus. Successful antireflux surgery offers complete and continuous reflux control, which is of particular relevance because intermittent pulse acid exposure causes greater cellular proliferation and de-differentiation of Barrett's oesophagus cells in culture than either no acid or continuous acid⁷. *In vivo* corroboration of this phenomenon is suggested by the Karolinska study² which found that acid suppression therapy increased the odds ratio threefold of patients with GORD developing adenocarcinoma. Two studies have shown a lower incidence of dysplasia and adenocarcinoma among patients treated by fundoplication. A study from the Mayo Clinic⁸, which followed 113 patients for up to 18 years, showed that no carcinomas occurred later than 39 months after fundoplication. The overall incidence of carcinoma was one in 274 patient-years of follow-up, compared with the corresponding mean figure of one in 80 from surveillance series on acid suppression therapy. These data do not support the belief that, because adenocarcinoma can still occur, fundoplication has no role in the management of Barrett's oesophagus. Rather, it should be acknowledged that the development of adenocarcinoma is inevitable once the cascade of genomic instability has commenced, but effective reflux control before this may have a protective role.

There is currently considerable interest in endoscopic mucosal ablation of the columnarized segment in association with pharmacological or surgical reflux control⁹. Argon plasma coagulation and photodynamic therapy using an oral photosensitizer result in a relatively superficial mucosal injury, whilst Nd-YAG laser and photodynamic

therapy using intravenous photoprin confer a deeper injury, with multipolar electrocoagulation intermediate between these. All are capable of producing squamous re-epithelialization, although complications, including perforation and stricture, may occur; this is particularly so with the methods that produce deeper injury. The presence of residual rests of metaplastic epithelium deep to the neosquamous epithelium has been reported with all techniques, being less prevalent with increasing depth of injury. Such rests are less amenable to superficial endoscopic biopsy, and retain the capability to progress to high-grade dysplasia and carcinoma.

The American College of Gastroenterology recommends regular endoscopic surveillance of patients with Barrett's oesophagus¹⁰, with the aim of detecting high-grade dysplasia as a precursor lesion to adenocarcinoma, although a focus of invasive adenocarcinoma is present in up to 40 per cent of patients at this stage. The rationale of endoscopic surveillance is to offer oesophagectomy, assuming the patient is fit, either before adenocarcinoma has developed or at an early stage, which results in a proportion of early lesions and 5-year survival rates both in excess of 80 per cent. Although endoscopic surveillance is widely practised in the USA, there is considerably less enthusiasm in the UK, where limited resources preclude a significant increase in workload for an overall benefit that has yet to be demonstrated. The principal deterring factors include the fact that only 3 per cent of affected patients die from adenocarcinoma, which may adversely influence cost-effectiveness. Furthermore, high-grade dysplasia has disadvantages as a marker of malignancy in that it occurs rather late in the transformation process, and is site-specific and so sampling error may occur. However, the development of optical coherence tomography, and various fluorescence techniques enabling accurate localization and characterization of abnormal cells according to their biochemical and molecular characteristics, will overcome many of these problems. Nevertheless, even current surveillance methods compare favourably from the standpoint of cost-effectiveness to both breast cancer screening and colon cancer surveillance. In the light of the risk factors outlined above, a selective surveillance policy, directed at those at greatest risk, would reduce the endoscopic burden and increase cost-effectiveness.

Traditionally, Barrett's oesophagus has only been deemed to exist if the circumferential columnarized segment exceeds 3 cm in length; this is to avoid confusion with junctional epithelium and to prevent overdiagnosis of the condition. However, it is now known that 'short-segment Barrett's' comprising circumferential columnarization less than 3 cm in length, or even confluent, non-circumferential 'tongues' (which are at least five times as

common as columnarization greater than 3 cm), can also progress to adenocarcinoma, although the risk is less. Application of the term 'short-segment Barrett's' and occasionally 'ultra-short-segment Barrett's' to the finding of microscopic intestinal metaplasia of the cardia, as seen in 18–36 per cent of patients presenting for upper gastrointestinal endoscopy, further increases the confusion, since this condition is more likely to be associated with *Helicobacter pylori* infection than GORD and has not been demonstrated to progress to cancer. It is unknown whether macroscopic 'short-segment Barrett's' progresses to long-segment disease, and lower risk of adenocarcinoma of the former makes surveillance even less cost-effective and more controversial in this context.

Several initiatives are underway to try to increase our knowledge in this difficult area. The UK National Barrett's Oesophagus Registry has recently been established, with the principal aims of studying regional and temporal variations in incidence of diagnosed cases, the natural history of the columnarized segment, and the influence of medical, surgical and endoscopic treatment. So far, almost 6000 cases from all over the UK are databased and some interesting findings have emerged. A prospective randomized study of the effect of optimal proton pump inhibition therapy and antireflux surgery, with or without endoscopic ablation, on the incidence of adenocarcinoma is ready to start if funded by the UK Medical Research Council, with 94 collaborating centres worldwide. The Karolinska study² has contributed to recommendations for a single screening endoscopy in patients over 50 years old with a reflux history greater than 10 years. It has also raised the question of possible prevention of Barrett's oesophagus by optimizing reflux control, particularly in the 25 per cent or so of patients in whom GORD is progressive. The other burning question, 50 years on, is whether the confusion, generated by applying an eponymous name to a condition now known to be so very different to that originally described, justifies the substitution of a more descriptive term, such as columnar-lined or metaplastic oesophagus. Furthermore, such a disease should probably be graded similarly to the Savary-Miller grading for oesophagitis, according to whether it is microscopic alone, confluent or circumferential, to reflect differing aetiology and behavioural characteristics.

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On getting started

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At some point, the fruits of your research labours must be turned into a final product, which will be read by a critical audience of potentially unlimited size.

Getting organized

To get a flow of words started, you must collect and organize materials, and create an environment free from interruptions. Nobody has produced a useful paper during the breaks in an operating list, no matter how slow the anaesthetist!

The correct environment for reading and writing is a combination of the right time and place. The task of collating the resources you require in an appropriate environment is an important one and there are key issues to be addressed at this stage. The most important is *time*. First thing in the morning, late at night, blocks of time each day or weekends will suit individuals differently but the creation of 'new time' to complete this task is highly desirable. You may have completed some other assignment which frees up this time. In general, most people are suited by dividing up work time into short blocks involving different tasks and this tends to increase efficiency.

Having a few self-imposed deadlines for completion of individual elements of the work is a useful discipline. Whether you prefer to write, type or dictate is a matter of personal preference. The spoken word may help to overcome the problem of 'writer's block' (see below) but it is important to remember that written and spoken languages are different and dictation for a written piece does not come easily to everyone. You will also find the consequence is that more editorial work will be required. The ability to rapidly 'cut and paste' with modern word-processing makes direct work on to the computer screen attractive to many.

Having decided on the right time, your next task is to find the right place. You may be able to produce the entire paper electronically, but most of us still like to scribble down occasional flashes of inspiration, which just happen to leap into the thought processes at sometimes inconvenient moments. It is worthwhile having a thesaurus or dictionary to hand, particularly for the phases when you rewrite and edit individual sections.

Ensure that your chosen environment will be comfortable, free from distractions and interruptions. A laptop

computer during a train or aeroplane journey may be popular, but it is probably the knowledge that there is a defined amount of time in a protected place that makes this so attractive.

While some individuals may find it is helpful to ritually organize their working environment, prolonged desk clearing is really just an act of procrastination appeasing an ill prepared mind.

Having set time aside and identified your working environment, you now need to gather together all of the reading matter (original scientific articles, published abstracts, review articles and text books) that you will need, along with materials concerned with the investigations you intend to report (grant applications, ethical submissions and study data). Whether you do this electronically or with paper is unimportant. It is vital, however, that the literature search should be exhaustive. Electronic searches of Medline and Embase are good starting points. Other electronic resources worth searching include the Cochrane Library, Scisearch and BIDS (Bath Information and Data Services). It is worthwhile at this stage investigating the resources available within your postgraduate or university library, where professional on-line searchers and medical reference librarians may be able to help with a search strategy. Medline goes back only to 1966. A library is still probably the easiest way to access most standard text books and obtain historical papers if they are relevant.

Taming the literature

Hopefully most of your reading was completed before you embarked on the project. In the light of your own research efforts, now is the time for a critical appraisal of this literature. Read, highlight and reread. Acquire additional references as a result and continue this process until you are certain that the bibliography upon which you intend to rely is exhaustive. You must learn to be critical and avoid the temptation to be selective or dismissive of material which contradicts your hypothesis or results. The use of a selective bibliography to reinforce a theory will nearly always lead to rejection by journal referees, if not major criticisms from your co-authors.

The development of this critical faculty is vital, not only for the process of writing but also in starting the entire

research process. Its importance cannot be overemphasized. An easy way to carry out a thorough appraisal of a publication is to ask six simple questions: why, how, who, what, how many and so what?

Why did the authors do the study? Is the hypothesis clearly stated? If the study involves some sort of therapeutic intervention, is it about efficacy or effectiveness? Efficacy is about a specific outcome under ideal circumstances whereas effectiveness seeks to determine whether an intervention does more good than harm in patients under normal clinical circumstances. Consider laparoscopic exploration of the common bile duct as a treatment for choledocholithiasis. To study efficacy, the treatment group will consist of patients with clearly documented stones in the bile duct, all of whom undergo laparoscopic surgery. To test efficacy, one might look at a simple short-term outcome such as the success rate of ductal clearance. When considering effectiveness, however, one is challenging not merely the intervention but the policy of using this intervention. Such a study would now have to involve all patients with bile duct stones, some of whom might not be fit for laparoscopic surgery. In addition, effectiveness involves consideration of a wider spectrum of outcomes, such as survival and quality of life. Surgical papers regularly confuse these issues. Be sure that you can recognize this confusion when it occurs.

How was the study conducted? Case series, before and after studies and randomized controlled trials probably represent an order of ascending scientific merit but even in a controlled trial you need to think about how patients were chosen and allocated.

Who was studied? Demographic data may be important. Was the study based on a small local population or individuals referred to a tertiary centre? Does the study represent the full spectrum of a disease? Are there clear inclusion and exclusion criteria?

What intervention and outcome measures were used? Compliance is important in most studies. Withdrawals, dropouts, crossovers and poor compliers all need to be considered, to see how much influence these factors might have had on the final results.

How many, refers to statistical significance and sample size. The most important question here is whether the authors considered the methods of analysis and necessary sample size before starting the study. Watch out for the popular trick of carrying out multiple analyses on a data set. This increases the likelihood that a significant result will be obtained by chance alone. Small sample size leads to trials

with weak power to detect important differences in outcome. The so-called type II statistical error is common in surgical papers, where the study is too small to detect statistically significant differences.

At the end of a paper, you must ask the question, so what? Is all of this of any real significance? A statistical increase in survival with chemotherapy for patients with advanced pancreas cancer may only need to be a few weeks, but is it really important or worthwhile?

Review articles require the same type of critical appraisal. There is a special issue here. Look out for the introduction of bias imposed by selectivity on the part of the author.

Writer's block

By now you will have begun to formulate ideas and hopefully have an outline in mind. You will probably begin with 'writer's block' but surprisingly this is not a bad thing, as it inhibits the generation of ill considered spontaneous rubbish. It is thought that writer's block is a form of internal criticism, where the words selected to express an idea are censored before they reach the page. It is a major problem for 'perfectionists' because it restricts the ability to formulate ideas in written words, even when such individuals have a clear grasp of these ideas. Thankfully it can actually be used to your advantage if you can switch it off in the manuscript drafting phase and switch it back on when editing.

Your first writing task is to create an outline which will lead to a first draft of the final paper. There is no need to be inhibited by writer's block at this stage because these words and phrases are unlikely to appear in the final document. The production of the outline can be achieved in a number of ways, usually as a flow chart with arrows leading from one point to the next or in a hub and spoke fashion around a central theme. Ultimately, it simply consists of a list of points which you feel will need to be included in the final document. It is from this draft outline that you can start to deal with sections of the paper. It is best to start with the easiest sections first rather than trying to go through the paper in a fixed order of introduction, methods, results and discussion. Methods and results are generally easier to write than the other sections. Tackling these may help to overcome writer's block. All of this helps the author to develop a flow of ideas, enabling the writer to convey a logical train of thought to the reader.

A bile duct stone cannot be found

A radiology report notes a stone at the bottom end of the common bile duct. At endoscopic retrograde cholangiopancreatography (ERCP) this stone is not found. Should one carry out a sphincterotomy or not? Mr Michael Thompson of Bristol, UK replies.

Endoscopic sphincterotomy carries short- and long-term risks. Before dividing the lower biliary sphincter a clear benefit should be anticipated. In this dilemma transabdominal ultrasonography is the most likely investigation to have triggered the ERCP. It is not a reliable test for ductal stones but, in conjunction with appropriate symptoms and gallbladder stones, a dilated duct may raise the suspicion of their presence. In the present instance the stone may have passed or, perhaps, it was never there in the first place; there exists also a small possibility that it has simply not been seen on the cholangiogram at ERCP. A decision has to be made instantly to proceed to sphincterotomy or to reconsider.

Cholangitis is a life-threatening condition in which good drainage of the duct is an immediate requirement and this should be provided by a sphincterotomy. The possibility of a residual stone perpetuating the problem can be overcome by the insertion of a stent, which will improve bile duct drainage still further. In severe acute gallstone pancreatitis much the same argument applies. If a stone is missed it is likely to be small and to pass through a sphincterotomy without rekindling the pancreatitis. If the pancreatitis is not severe, no duct stone is seen and the patient is recovering, a cholecystectomy rather than a sphincterotomy is the appropriate treatment.

Other, occasional and rather individual circumstances can occur in which a sphincterotomy may carry less risk than a missed stone. For example, an immunosuppressed patient with other co-morbidity may represent a considerable risk for cholecystectomy. However, such situations are rare and judgement is, inevitably, difficult. Passage of the offending duct stone in a jaundiced patient is marked by a patulous, ragged and reddened ampulla that is usually easy to cannulate. Together with an 'empty' duct on the cholangiogram, this feature makes it almost certain that a stone was present and has passed. Sphincterotomy can be avoided and a cholecystectomy performed.

One of the major advantages of endoscopic sphincterotomy is in the treatment of bile duct stones in the frail or infirm patient for whom cholecystectomy is unlikely to be realistic. A search for duct stones is usually undertaken after an episode of jaundice or pancreatitis in these patients. If the duct is empty, any offending stone must be assumed to have

passed spontaneously. A number of small, uncontrolled, observational studies report a low rate of recurrent pancreatitis after sphincterotomy. There is therefore some justification for the performance of a sphincterotomy under these circumstances but, in the absence of good randomized trials, my own innate conservatism makes me a little reluctant. There is an increasing body of opinion that cholecystectomy should be undertaken if at all possible in patients with current or passed bile duct stones. Even relatively unfit patients seem to do well and the result is a complete treatment of the gallstone problem.

Currently, the elective treatment of gallstones is dominated by laparoendoscopic methods. Many patients undergoing cholecystectomy have a preliminary elective (or possibly postoperative) ERCP. If this fails to find a stone, sphincterotomy is not justifiable; it can be assumed that the stone has passed. The cholecystectomy should be completed at the earliest possible time to prevent the further migration of stones down the bile duct; an operative cholangiogram may help remove any doubt about bile duct stones. If there is concern about the status of the bile duct in the presence of gallbladder stones it is important not to forget the possibility of pancreatic or biliary cancer being the cause.

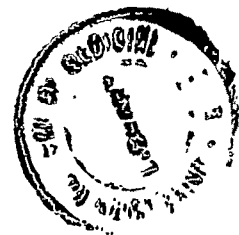
The situation experienced by the endoscopist in the present dilemma should be avoided if possible. If there is a long delay after the first test that suggested a bile duct stone, that test may be worth repeating before undertaking ERCP. Bile duct stones represent a dynamic rather than a static arrangement and my experience is that well over half of all bile duct stones pass spontaneously, often unnoticed. If the report of a duct stone is recent, it is worth assessing the degree of confidence of the radiologist. Should this confidence be unshakeable, the next step depends on the proposed treatment of any stone. If the patient is inevitably to have a cholecystectomy, my own choice would be to carry out operative cholangiography. Laparoscopic ultrasonography may be used at this point. If a stone is confirmed, the duct can be explored laparoscopically. Good results, with duct clearance rates in excess of 90 per cent, are now being reported. Should this fail, conversion to open operation is a good option in the younger patient as it preserves the lower biliary sphincter. Endoscopic sphincterotomy, on the other hand, is associated with poor long-term results due to duodenobiliary reflux (although good descriptions of the long-term results of supraduodenal exploration are not numerous).

When a radiologist is uncertain of his or her findings, a continuing non-invasive approach should be adopted if possible. Magnetic resonance cholangiopancreatography seems likely to supplant ERCP as the best investigation for the bile duct. Endoscopic ultrasonography and computed tomographic cholangiography appear satisfactory alternatives. If these are negative, cholecystectomy can proceed and ERCP is avoided. Investigative, as opposed to therapeutic, ERCP appears to be coming to the end of its natural life and its use as the first, or even second, avenue of investigation should be avoided.

There are several exciting changes occurring in the management of bile duct stones. In the near future we will see a decline in the use of ERCP and interest in sphincter preservation. Speculative sphincter destruction should have only a very small role in patient management.

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Laparoscopic surgery and surgical infection

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Introduction: It has been observed that the metabolic response to surgical injury is less after laparoscopic surgery than after open surgery. However, the effect of laparoscopic surgery on surgical infection has not been given much attention in the surgical literature, even though it may decrease the incidence of infectious complications. The objective of this study was to assess the influence that laparoscopic surgery has on surgical infection and to highlight certain controversial aspects.

Methods: A review of the literature was undertaken to examine the relationship between laparoscopic surgery and surgical infection. This was achieved primarily by using PubMed Medline as a source of material.

Results and conclusion: Laparoscopic surgery is associated with better preservation of the immune system than open surgery. This results in a decreased incidence of infectious complications. Although carbon dioxide pneumoperitoneum affects the peritoneal response to injury, it seems to have no harmful effect in terms of intra-abdominal infection. Nevertheless, at laparoscopic operation the virulence of intestinal micro-organisms should be recognized and, while knowing the advantages of minimally invasive surgery, the surgeon should consider the complexity of this technique. Furthermore, maintenance of laparoscopic instruments should be governed by the same norms as those used in open surgery; recommendations offered by the manufacturers should be respected.

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Introduction

The success of laparoscopic surgery has led to the re-evaluation of many long-accepted surgical doctrines. Certain therapeutic standards, such as postoperative guidelines or diet restriction, and surgical habits, such as the placement of subhepatic drains or use of T tubes, have been modified. Pathophysiological aspects such as metabolic, inflammatory and immunological responses to surgery have become areas of new interest. A lower incidence of complications and a better postoperative outcome have often been observed with laparoscopic surgery compared with conventional open operation. While the impact of the former on surgical infection has so far been given little attention, laparoscopy may modify its incidence and the characteristics of such infection (*Table 1*). The aim of this review is to assess the influence that laparoscopic operation has on surgical infection and to highlight certain controversial aspects that exist at present.

Impact of laparoscopic surgery on immune response

Surgical intervention triggers a series of alterations in the immune system and therefore in the inflammatory response¹. Any immune suppression occurring after trauma is related to an increase in the incidence of septic complications¹. It is now broadly accepted that the immune system is better preserved following laparoscopic than open surgery; this is demonstrated by the diminished release of various markers including interleukin (IL) 6 and C-reactive protein (CRP). This decreased immune response results from a significantly smaller tissue injury². Recent studies have analysed this topic thoroughly^{3–5}, describing the effect that laparoscopic surgery has on different components of the immune system, such as T-cell lymphocytes and delayed hypersensitivity³, mononuclear phagocytic neutrophils⁶, polymorphonuclear elastase⁷ and anion superoxide⁸. All exhibit greater alterations following open surgery. Apart from the above, it is also important to analyse the peritoneal

Table 1 Aspects of laparoscopic surgery that may influence surgical infection

Impact on the immune system
Influence of pneumoperitoneum and gas on peritoneal inflammatory response
Use of antibiotic prophylaxis
Influence of pneumoperitoneum and gas on a pre-existing infection
Infrequent infectious complications potentially related to laparoscopic surgery
Pneumoperitoneum as a catalyst of infection
Technical aspects related to infection (instruments and sterilization)

response to infection because surgical infection initially develops in the peritoneal cavity.

Influence of pneumoperitoneum on the peritoneal inflammatory response

Pneumoperitoneum exercises a direct dual effect on the peritoneal defence system. The first relates to the mechanical distension of the peritoneal lining and the second results from the type of gas used. Pneumoperitoneum causes morphological changes in the peritoneal microstructure, proportional to its duration of use. These changes cannot generally be observed during open operation. Loss of contact and fissures between mesothelial cells, as well as infiltration of macrophages and erythrocytes, have been demonstrated by electron microscopy^{9,10}, features that occur at a faster rate in a contaminated environment¹¹.

West *et al.*^{12,13} investigated the production of cytokines by peritoneal macrophages incubated in carbon dioxide. The production of tumour necrosis factor and IL-1 in response to bacterial endotoxin was less than that in a helium environment, and these authors suggest that carbon dioxide affects intracellular conditions, creating an acidic milieu. These findings were confirmed by Wunsch *et al.*¹⁴ upon observing that rats insufflated with carbon dioxide attained a significantly lower intra-abdominal pH than those insufflated with ambient air or helium. Therefore, carbon dioxide may impair the cellular physiology of macrophages. However, Iwanaka *et al.*¹⁵ observed an increased number and greater viability of peritoneal macrophages in carbon dioxide pneumoperitoneum as opposed to conventional laparotomy. They also found that the amount of cytokines and nitrous oxide released was less in the laparoscopic group¹⁶, interpreting their results to be a consequence of greater cellular stress during open surgery and not, in contrast to the results of West and colleagues, as an anomaly in the function of macrophages. In another study, Evrard *et al.*¹⁷ evaluated the effect of carbon dioxide on cellular immunity in the entire peritoneal system, arguing that the viability of T cells depends on pH level.

However, no significant changes were demonstrated after the use of pneumoperitoneum. Finally, Watson *et al.*¹⁸ evaluated the effect of different factors in ambient air on inflammatory response during surgery. They observed a decrease in phagocyte activity with open surgery in comparison to laparoscopy. They concluded that lipopolysaccharide was the inducing factor because mixing carbon dioxide with this substance gives similar results in open surgery.

These results lead the authors to believe that both the mechanical factor and the direct influence of carbon dioxide affect peritoneal cell physiology. The peritoneal cell mechanism, however, displays better preservation during laparoscopic than during open surgery. The advantages of using gases other than carbon dioxide are still under investigation.

Effect of laparoscopic operation on peritoneal infection

In previous years laparoscopic exploration was generally conducted solely for diagnostic purposes and was consequently of short duration. However, the application of operative laparoscopy requires pneumoperitoneum at high pressure for a prolonged period. This has caused concern that hyperpressure of such duration may increase intra-peritoneal infection by peritoneal dissemination or by some other mechanism. During a clean or a clean-contaminated intervention, such as laparoscopic cholecystectomy, peroperative contamination occurs in up to 30 per cent of cases as a consequence of gallbladder rupture. When laparoscopic surgery is used for emergencies such as appendicitis or cholecystitis, the operation is performed in the presence of a pre-existing intra-abdominal infection. However, the incidence of postoperative infectious complications is generally assumed to be low.

Incidence of infectious complications during clean and potentially contaminated laparoscopy

An analysis of different clinical studies on laparoscopic procedures has shown a lower occurrence of intra-abdominal and wound infection than that following open surgery. In 1518 patients undergoing laparoscopic cholecystectomy the incidence of wound infection was 1.1 per cent and there were only two intra-abdominal abscesses (0.1 per cent)¹⁹. Gold-Deutch *et al.*²⁰ studied the incidence of septic complications in a series of 247 laparoscopic cholecystectomies. They obtained bile samples for microbiological analysis and in 13 per cent of cases cultures were positive, yet only two patients developed umbilical trocar infection (0.8 per cent). These results differed from those

observed during open cholecystectomy, in which the incidence of wound infection was between 2 and 7 per cent²¹. Similar outcomes were obtained for laparoscopic operations for colorectal disease (Table 2)^{22–26}.

Antibiotic prophylaxis is generally well established in clinical practice²⁷. However, the low occurrence of abdominal wall infection after laparoscopic surgery suggests that its role in such procedures needs to be re-evaluated. Few studies have analysed this topic and so data are not as conclusive as for open surgery. Frantzides and Sykes²⁸ compared 164 patients treated laparoscopically, who received preoperative antibiotic prophylaxis, with 78 patients who were not administered antibiotics; the differences in infection rate were not significant (nine of 164 *versus* none of 78 respectively). Manger and Wolff²⁹ compared retrospectively the number of abdominal wall infections in patients who received antibiotics with that for those who did not receive prophylaxis. They reported a higher incidence of infection in those not administered antibiotics (one of 100 *versus* six of 100). Conversely, two further investigations^{30,31} carried out prospective and randomized studies comparing a placebo with a treated group. There was no difference between the groups in terms of infection and the authors concluded that prophylaxis can be omitted, at least in the case of simple gallstones. It is also important to emphasize that the clinical consequences of

trocar wound infection are much less significant than those of infection of a large laparotomy incision. Late sequelae of infectious complications, such as incisional hernia, are also of lesser clinical importance.

Laparoscopic surgery and the spread of already established infection

Appendicitis, perforated duodenal ulcer and colonic diverticulitis are situations in which an intra-abdominal infection pre-exists. The first question that arises is whether a carbon dioxide environment has an effect on the progression of peritonitis, possibly by causing dissemination in the abdominal cavity, bacteraemia and septic shock. The mechanism that facilitates the spread of bacteria is not yet well understood. It is suggested that lymphatic lacunas located in the diaphragm may aid in bacterial spread^{32,33}. The peritoneum also reacts to inflammation by causing a contraction of mesothelial cells, which in turn produces an aperture between their intercellular junctions. This facilitates the passage of micro-organisms. Furthermore, the high intra-abdominal pressure causes an augmented pressure gradient as well as a physical distension of the diaphragm, which both favour the passage of bacteria. Morphological studies have confirmed this by electron microscopy^{8–10,34}. Consequently, the risk of bacteraemia or sepsis is potentially increased by the laparoscopic environment.

It is generally assumed that laparoscopic surgery carried out in a septic environment is safe. However, precise clinical information on outcome in terms of progression and degree of peritonitis as well as duration of intervention does not yet exist. However, such information is key in assessing the possible harmful effect of pneumoperitoneum on intra-abdominal infection.

Two recent meta-analyses of prospective and randomized studies comparing open surgery with laparoscopic operation showed that laparoscopic appendectomy resulted in a significant reduction in septic complications (odds ratio 2.6, $P < 0.003$)^{35,36}. The incidence of septic

Table 2 Incidence of intra-abdominal and wound infection after laparoscopic colectomy

Reference	Year	No. of patients	Wound infection (%)	Intra-abdominal infection (%)
Agachan <i>et al.</i> ²²	1996	167	4.7	1.7
Wexner <i>et al.</i> ²³	1996	140	2.8	2.8
Fielding <i>et al.</i> ²⁴	1997	359	3.3	0.6
Lacy <i>et al.</i> ²⁵	1997	118	2.5	—
Köckerling <i>et al.</i> ²⁶	1998	500	3.4	—

Table 3 Results of laparoscopic treatment of acute peritonitis

Reference	Year	n	Pathological diagnosis				Morbidity					
			Appendicitis	PDU	Cholecystitis	Other	Conversion	Overall	Sepsis	Septic shock	Reoperation	Mortality
Geis and Kim ³⁷	1995	149	117 (78.5)	4 (2.7)	7 (4.7)	21 (14.1)	5 (3.4)	—	—	—	—	1 (0.7)
Cueto <i>et al.</i> ³⁸	1997	107	20 (18.7)	4 (3.7)	15 (14.0)	68 (63.6)	13 (12.1)	23 (21.5)	10 (9.3)	2 (1.9)	8 (7.5)	5 (4.7)
Henry <i>et al.</i> ³⁹	1998	200	109 (54.5)	14 (7.0)	52 (26.0)	25 (12.5)	26 (13.0)	17 (8.5)	7 (3.5)	0 (0.0)	2 (1.0)	0 (0.0)
Navez <i>et al.</i> ⁴⁰	1998	231	91 (39.4)	69 (29.9)	—	71 (30.7)	34 (14.7)	31 (13.4)	10 (4.3)	2 (0.9)	5 (2.2)	9 (3.9)

Values in parentheses are percentages. PDU, perforated duodenal ulcer.

shock as a consequence of peritonitis does not appear to be increased with the laparoscopic technique (Table 3)³⁷⁻⁴³. In a study conducted by Navez *et al.*⁴⁰, only two (0.9 per cent) of 231 patients who had a laparoscopic operation for peritonitis developed postoperative septic shock. Geis and Kim³⁷ analysed 115 patients with abdominal infection, the majority of whom had acute appendicitis. Ninety-six per cent were treated laparoscopically and the incidence of postoperative septic morbidity was no greater than that after conventional open surgery. Benoit *et al.*⁴¹ and Sezeur *et al.*⁴² investigated the occurrence of bacteraemia after laparoscopic appendectomy and concluded that there was no increase in infectious morbidity compared with open surgery.

The second question that arises is whether laparoscopic surgery maintains its advantages of minimal invasiveness that have been established in clean surgery, such as less tissue damage. Lau *et al.*⁴⁴ analysed the metabolic response to laparoscopic operation, comparing two groups of patients with perforated duodenal ulcer treated by laparoscopy or open surgery. The incidence of endotoxaemia and bacteraemia was low in both groups and the changes in variables such as IL-6, CRP and cortisol levels were similar.

Thus, the inflammatory response seems to be quantitatively more affected by infection than by the tissue injury resulting from laparoscopy.

Influence of pneumoperitoneum pressure on intra-abdominal sepsis: experimental studies

Many aspects of laparoscopic surgery and its relationship to infection are difficult to investigate in humans, which has led to experimental studies on animals. These have focused on the effect of pneumoperitoneum on the growth and translocation of bacteria in two different situations: (1) in a pre-existing abdominal infection and (2) in peroperative intraperitoneal contamination. Both the physical effect of hyperpressure and the influence of the gas have been analysed. Other variables that have been investigated are time of onset of infection, degree of progression of infection, and duration of pneumoperitoneum. Unfortunately, the results are of limited value because the studies were conducted with different bacterial strains and there was a lack of unanimity in design^{45,46}.

The use of laparoscopy in a situation of pre-existing intra-abdominal infection has been investigated extensively in

Table 4 Results of experimental studies on the effect of pneumoperitoneum on intraperitoneal infection

Reference	Year	Animal	Experimental model	Bacteria	Evolution time	Duration of pneumo-peritoneum	Experimental groups	Bacteraemia	Peritoneal bacterial count
Gurtner <i>et al.</i> ⁴⁷	1995	Rabbit	Peritonitis	<i>E. coli</i>	60 min	60 min	LS v LT	No difference	
Collet <i>et al.</i> ⁴⁸	1995	Pig	Peritoneal contamination	<i>E. coli</i>	8 h	60 min	LS v LT		LT > LS
Bloechle <i>et al.</i> ⁴⁹	1994	Rat	Gastric perforation	Mixed	6, 9, 12, 24 h	60 min	LS v control	12 and 24 h, LS > LT	12 and 24 h, LS > LT
Dugue <i>et al.</i> ⁵⁰	1995	Rat	Pentontitis, ileal perforation	Mixed	24 h	60 min	LS v control	No difference	
Ozguc <i>et al.</i> ⁵¹	1996	Rabbit	Peritonitis	<i>E. coli</i>	60 min	60 min	LS v LT	No difference	
Evasovich <i>et al.</i> ⁵²	1996	Rat	Pentontitis	<i>E. coli</i>	180 min		LS v control	LS > control	
Bustos <i>et al.</i> ⁵³	1997	Rabbit	Pentontitis, perforation of occluded ileum	Mixed	6 h	60 min	LS v control	LS > control	
Jacobi <i>et al.</i> ⁵⁴	1997	Rat	Pentontitis, faeces	Mixed	1 h, 2 and 7 days	30 min	LS v LT	No difference	Abscesses, LT > LS
Sare <i>et al.</i> ⁵⁵	1997	Rat	Pentontitis	<i>E. coli</i>	8 h		LS v LT v control		LS > LT > control
Jacobi <i>et al.</i> ⁵⁶	1998	Rat	Pentontitis, faeces	Mixed	60 min	30 min	LS v LT	LT > LS	
Bloechle <i>et al.</i> ⁵⁷	1998	Pig	Gastric perforation	Mixed	6 and 12 h	60 min	LS v LT	12 h LS > LT	
Ipek <i>et al.</i> ⁵⁸	1998	Rat	Pentontitis, caecostomy	Mixed	1, 3, 6 h	30 min	LS v control	6 h LS > control	LS > control
Balagué <i>et al.</i> ⁵⁹	1999	Rat	Pentoneal contamination	<i>E. coli</i>	0 min	30 min	LS v LT v WLL v control	LT > LS	LT > LS
Ozmen <i>et al.</i> ⁶⁰	1999	Rabbit	Pentoneal contamination	<i>E. coli</i>	6 h	60 min	LS v LT	LS > LT	
Palombo <i>et al.</i> ⁶¹	1999	Pig	Pentontitis	<i>E. coli</i>	24 h		LS v LT	No difference	

LS, laparoscopy, LT, laparotomy, WLL, wall lift laparoscopy; v, versus; *E. coli*, *Escherichia coli*

experimental studies (Table 4)^{47–61}. One of the most controversial areas is the application of laparoscopic operation to treat gastroduodenal perforation. Bloechle *et al.*^{49,57} analysed the effect of pneumoperitoneum on peritonitis secondary to gastric perforation in a rat and a pig model. In both, use of pneumoperitoneum 6 h after perforation resulted in a significant increase in the number of bacteria in peritoneal and blood cultures^{52,55,58}. However, other experimental models have not been able to demonstrate that pneumoperitoneum influences the spread of bacteria in blood^{47,50,51}; these studies were conducted with a single bacterial strain, which is clinically improbable. Jacobi *et al.*^{54,56} therefore developed a multibacterial peritonitis by inoculating rats with faeces. They observed that the systemic inflammatory response and the number of intra-abdominal abscesses were lower after laparoscopic surgery than after open operation (laparotomy).

It is also important to investigate the effect that pneumoperitoneum has on the haemodynamics of septic shock. Greif and Forse⁶² evaluated haemodynamic modifications induced by pneumoperitoneum in a pig model with endotoxic shock. They observed that pneumoperitoneum produced hypercapnia and acidosis, and lowered the cardiac index. These results suggest caution when proposing laparoscopic surgery for patients with profound sepsis. Recuperation of intestinal motility in septic environments has also been analysed in laparoscopic surgery and in open procedures. Ishikawa *et al.*⁶³ investigated intestinal motility after laparoscopic cholecystectomy in dogs with and without peritonitis. They observed a slowing of motility in the infected group.

Progression of peritoneal contamination during laparoscopic surgery has also been analysed. Balagué *et al.*⁵⁹ carried out an experimental study to evaluate the inflammatory response to intra-abdominal contamination produced during operation. They designed an experimental study on mice, dividing the animals into four groups: controls, laparotomy, carbon dioxide laparoscopy, and wall lift laparoscopy. Intra-abdominal contamination was induced with *Escherichia coli*. Peritoneal fluid and blood samples were analysed, and both peritoneal and systemic levels of cytokines were measured. The results indicated that the peritoneal response to sepsis is better preserved after laparoscopy than after open surgery, and that carbon dioxide does not seem to influence bacterial growth. Collet *et al.*⁴⁸ obtained similar results in an experimental study on pigs that were subjected to a Nissen fundoplication by both laparoscopy and open surgery, with intraoperative inoculation of *E. coli*. They concluded that there was a greater elimination of bacteria from the abdominal cavity after laparoscopy. Bustos *et al.*⁵³ observed that the progression of

peritonitis was worse after intestinal perforation with occlusion as opposed to perforation without occlusion. Type and quantity of inoculation, therefore, are intrinsically related to the effect that pneumoperitoneum has on peritoneal inflammatory response.

Effects of the gas used in pneumoperitoneum on bacterial peritonitis: experimental studies

It has been demonstrated that the smoke produced by electrocauterization is able to spread viable cells and viruses. Taffinder *et al.*⁶⁴ investigated whether carbon dioxide pneumoperitoneum with a pre-existing abdominal infection permits the transport of bacteria through the abdominal cavity during operation. They analysed the presence of bacteria in gas aspirated from the abdominal cavity after laparoscopic intervention in 32 controls and in 21 patients with an evident intra-abdominal septic focus. The control group showed positive cultures of peritoneal lavage in 3 per cent of cases, whereas cultures in the second group were positive in 30 per cent. Only one of the 106 carbon dioxide cultures was positive and so the authors concluded that pneumoperitoneum alone was not able to produce bacterial dissemination.

Carbon dioxide used to maintain expansion of the abdominal cavity during laparoscopic work may influence bacterial growth. Several studies have been conducted to determine whether carbon dioxide may have a bactericidal or bacteriostatic effect. Champault *et al.*⁶⁵ studied the effect of this gas on the growth of *E. coli* and *Staphylococcus aureus* colonies. They observed a delay in the growth of bacteria and so attributed a bacteriostatic effect to carbon dioxide. However, Miner and Levine⁶⁶ subjected colonies of *E. coli* and *S. aureus* to a carbon dioxide environment under similar conditions and did not find any differences compared with controls. *E. coli* is a facultative anaerobe, which may influence results.

Infrequent infectious complications potentially related to laparoscopic surgery

Several infectious complications, especially at the level of the abdominal wall, have been described after laparoscopic cholecystectomy, perforated duodenal ulcer surgery and hysterectomy^{67–73}. Factors that may aggravate serious infections, such as gas gangrene or necrotizing fasciitis, include prolonged intervention, anaerobic conditions and dissection of musculoaponeurotic tissue (where carbon dioxide may become trapped). García Olmo and colleagues⁶⁷ described a case of gangrenous peritonitis following laparoscopic cholecystectomy, in which no intra-abdominal infectious focus was found. However, such cases

are rare and data are insufficient to conclude that laparoscopic surgery carries an increased risk of infection compared with open surgery.

Pneumoperitoneum-related infection

A possible danger of infecting surgical personnel has been attributed to the use of pneumoperitoneum. Suspended particles from the internal cavity may travel from the body through trocar orifices into the ambient air. Evidence exists that particles of carbonized material created by electrocauterization may be able to transport viral elements and viable cells⁷⁴. However, carbon dioxide alone has little capacity to allow viable bacteria to become airborne^{64,75}. There is a consensus, however, that a small risk of infection through aerosolization during interventions with pneumoperitoneum may exist when dealing with patients who are infected with human immunodeficiency virus (HIV) or hepatitis C virus. This risk is smaller than that associated with a cutaneous puncture, yet it is recommended that the situation be avoided by aspirating the intra-abdominal gas at the end of the procedure. A potential risk of contamination may also come from the carbon dioxide insufflator, because micro-organisms are able to grow inside the connecting tube. It is therefore recommended that filters are used that impede the passage of viable elements⁷⁶.

It is important to consider the use of laparoscopic surgery when treating individuals who are HIV positive⁷⁷⁻⁷⁹. Because of its smaller clinical impact, laparoscopic surgery is preferred to open operation when abdominal exploration for acute abdomen is needed in such patients. It is also recommended for other therapeutic interventions such as cholecystectomy or splenectomy, as risk of infection to the surgical team is minimal. However, it is important to stress the need to aspirate the pneumoperitoneum at the end of the procedure and to discard or sterilize used instruments.

Technical aspects related to surgical infection (instruments and sterilization)

Knowledge about how infection can be transmitted by way of instruments is an important factor in its prevention. For open surgery, instruments are easily sterilized by conventional methods (gas or autoclave). However, for laparoscopic work the kit is mechanically more complex and so its complete sterilization is difficult; disposable instruments are preferred. Nevertheless, because of cost, surgeons have reused laparoscopic equipment despite it not having been designed to be so handled. Fortunately, postoperative infection as a result of repetitive use has not so far been reported and several studies have demonstrated that, despite the difficulty in cleaning, the equipment is infection-

proof⁸⁰⁻⁸². This is not, however, an argument for reuse, since solid residue exists in higher quantity following sterilization of instruments used for laparoscopic work. Given today's great medicolegal pressures, it is recommended that surgeons follow manufacturers' instructions. Reusable instruments, on the other hand, are able to be dismantled to allow complete cleaning and sterilization.

Conclusion

The smaller biological impact induced by laparoscopy is followed by a greater preservation of the immune response than that after open operation, consequently lowering the incidence of infectious complications. Although carbon dioxide pneumoperitoneum influences the mechanisms of the peritoneal response, it does not appear to have a harmful effect in terms of intra-abdominal infection. However, the aetiology and progression of peritonitis, the virulence of intra-abdominal micro-organisms, and the duration of intervention are factors to be taken into account when applying this surgical technique. The surgeon should value the potential advantages of the minimally invasive approach, while acknowledging its technical complexity, so that patients may benefit. Secondary complications that may arise in a septic environment must be avoided. Finally, the maintenance of laparoscopic instruments should be governed by the same guidelines as those used in open surgery; manufacturers' recommendations should be respected.

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Sportsman's hernia

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Background: Sportsman's hernia is a debilitating condition which presents as chronic groin pain. A tear occurs at the external oblique which may result in an occult hernia. The definition, investigation and treatment of this condition remain unclear.

Methods: A systematic Medline search was performed and all literature pertaining to chronic groin pain, groin injury, sportsman's hernia and sportsman's groin from 1962 to 1999 was retrieved for analysis.

Results: The costs of computed tomography and magnetic resonance imaging are such that their routine use for assessment of patients with groin pain cannot be justified. They may, however, be employed in difficult cases to help define the anatomical extent of a groin injury. Plain radiography, ultrasonography and scintigraphy should be the usual first-line investigations to supplement clinical assessment. Herniography may help in situations of obscure chronic groin and pelvic pain. There is no consensus view supporting any particular surgical procedure for sportsman's hernia. A number of reports have been published describing different repairs of the posterior inguinal wall deficiency. Appropriate repair of the posterior wall results in therapeutic benefit in selected cases.

Conclusion: The diagnosis of sportsman's hernia is difficult. The condition must be distinguished from the more common osteitis pubis and musculetendinous injuries. Early surgical intervention is usually, although not always, successful when conservative management has failed.

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Chronic groin pain is a major diagnostic and therapeutic dilemma. It is responsible for a significant time away from work and sports competition¹, with a reported incidence between 0.5 and 6.2 per cent^{2–5}. Groin injury is particularly common in football players, at least 58 per cent of whom give a history of previous sports-related groin pain⁶. Recurrent groin strain is also common, both in football and hockey players; 6 per cent will suffer at least one episode per season⁵. Over the past decade the number of sports-related injuries has increased as a function of increased athletic activities⁷, and the demand for an early return to work and competitive sport puts pressure on the doctor for immediate diagnosis and treatment. A Swedish study reported that in 50 per cent of patients groin pain persisted for over 20 weeks after the causal injury³.

Groin injury leading to chronic pain is often referred to as the sportsman's hernia⁸ or groin disruption⁹ and, sometimes, as pubalgia¹⁰. In many cases, clinical signs are lacking despite the patient's symptoms and there is

known to be a high incidence of symptomatic impalpable hernia in patients with obscure groin pain (36–84 per cent)^{4–11}. Gilmore popularized the syndrome of groin disruption as 'Gilmore's groin' in the early 1990s and has reported good results from surgical management¹². Since then many studies have reported a success rate with surgical intervention of 63–90 per cent^{13–18}. A recent leading article in this Journal has highlighted the diagnostic difficulty associated with chronic groin pain, especially in the sportsman¹⁹.

Method

A systematic Medline search was performed and the literature pertaining to chronic groin pain, groin injury, sportsman's hernia and sportsman's groin from 1962 to 1999 was retrieved. Further articles, identified from the reference lists of these papers, were also selected and reviewed. Fewer than 40 articles adequately discuss the management of chronic pain in sportsman's hernia.

Pathophysiology

The anatomy of groin hernias is well described in standard surgical textbooks. Chronic groin pain may originate from muscles, tendons, bones, bursas, fascial structures, nerves and joints²⁰. In the inguinal canal, the absence of striated muscle at the posterior inguinal wall and the passage of the spermatic cord predispose the abdominal wall to weakness. The guard mechanism of the inguinal canal against abdominal pressure proves insufficient in the case of indirect inguinal hernia. Fruchaud²¹, a French surgeon and anatomist, described the musculopectineal gap as a weak area in the deep plane covered only by the transversalis fascia, forming the posterior inguinal wall of the abdomen. Here the transversalis fascia provides the only resistance to intra-abdominal pressure. Stoppa and Van Hee²² described this area as the herniogenic vocation region.

A deficiency of the posterior inguinal wall is the commonest operative finding in patients with groin pain^{8,18}. The deficiency presents as a bulge in the posterior wall and is found in 80–85 per cent of those who have undergone herniorrhaphy for chronic groin pain^{8,18}. Gullmo²³ suggested that pain in these circumstances may be caused by a distension of the peritoneum or stretching of the ilioinguinal nerve. Zimmerman²⁴ suggested that a tear in the conjoint tendon may be the cause of the bulge in the posterior wall and that occult hernia may be a cause of footballer's groin pain. In Gilmore's description of groin disruption, a torn external oblique aponeurosis causes dilatation of the superficial inguinal ring. Together with a torn conjoint tendon, this may cause a dehiscence between the inguinal ligament and the conjoint tendon¹².

Lovell *et al.*²⁵ reported an incidence of incipient hernia of 50 per cent in their series of 189 athletes. One herniography study revealed a symptomatic impalpable hernia in 51 per cent of male and 21 per cent of female patients¹³, and another study reported a hernia in 84 per cent of elite athletes with groin pain¹¹. Ekberg⁴ described a lower figure (36 per cent) in patients presenting with obscure groin pain. It is also of interest that Hess²⁶ noted oedema of the spermatic cord at the time of surgery. Berliner²⁷ biopsied the transversus abdominis aponeurosis in patients with a direct inguinal hernia and a strong family history of inguinal hernia, and found fragmentation and paucity of elastin fibres.

Clinical findings

Although debilitating, groin pain is often vague, leading to a delay in diagnosis. An accurate clinical history and extensive examination of the spine, pelvis, hips, and abdominal and

leg musculature plays an important part in determining its cause. The site, duration and nature of the pain should be noted, along with urological symptoms, skeletal problems and rheumatological disorders. Initial symptoms may be minimal and there is some debate about the best time for physical examination of the patient. Hackney¹⁷ argues that this may be after return to exercise and return of the pain.

Polglase *et al.*¹⁸ reported that 59 (92 per cent) of 64 patients presented with a slow onset of pain over a period of time, ranging from 1 to 6 months; the remainder complained of sudden onset. Loftus *et al.*²⁸ noted that only three (5 per cent) of 63 patients with herniograms had a hernia clinically palpable before exploration; six of 26 had a cough impulse. Diagnostic problems may occur owing to variability in the distribution of the pain and the precise local pathology. Pain is notably worse over the pubic tubercle of the affected side, and the area around the external ring is tender¹⁷. Gilmore described chronic pain that was aggravated by sudden and twisting movements¹². Coughing, sneezing and kicking a ball exacerbate the symptoms. Clinical findings typically include a lack of visible external signs in the affected groin, dilatation of the superficial ring (demonstrable by scrotal inversion with the tip of the little finger), a cough impulse and marked tenderness in the opposite groin¹².

Differential diagnosis

The incidence of multiple pathological causes of groin pain is said to be high and may be relevant in up to a quarter of chronic groin pain sufferers^{25,29}. This may account for some of the treatment failures. Several comprehensive reviews have also highlighted the wide variety of causes of groin pain^{24,30,31} and inadequate treatment may lead to recurrent problems. Apart from hernia, two other major causes of groin pain are muscle and tendon injury, and osteitis pubis²⁰. Other less common causes include nerve entrapment and urological pathology. Rarer reported causes include bone and joint disease, such as stress fractures, snapping hip syndrome, spondylolisthesis, early osteoarthritis and slipped upper femoral epiphysis¹⁷.

Muscle and tendon injury

Strain of the muscle–tendon unit is the most common type of injury causing disability in sport³². It occurs mainly at the proximal end, either to the tendon itself or to the musculotendinous junction in the muscle belly³³. The adductor tendon is often involved, especially adductor longus; other muscles likely to be affected include rectus femoris and the rectus abdominis muscle and tendon. The

history is a good guide to identifying muscle and tendon injury. Plain radiography is often normal in muscular injuries of less than 1 week's duration³³. The role of computed tomography (CT) is unclear as its ability to detect acute muscle injury is limited¹⁸ but it may be of use in chronic or recurrent injury. Magnetic resonance imaging (MRI) is able to characterize muscular or musculotendinous injuries better than CT and it can outline the extent of injury within the muscle group³³. Ultrasonography has also been used to identify such injuries.

Osteitis pubis

Osteitis pubis is especially common in sports that involve kicking or physical contact, especially football, with a reported radiological incidence in soccer players of 14–28 per cent¹⁴; there is a higher incidence in more competitive athletes⁶. This injury results from repetitive avulsive trauma near the pubic symphysis, usually involving the adductor muscles or gracilis. The clinical picture includes focal pain or tenderness at the pubic symphysis in 70 per cent of confirmed cases³⁴, with occasional adductor muscle tenoperiostitis. The history may include a direct blow to the symphysis or pelvic instability from a sacroiliac joint injury.

Radiological changes of osteitis pubis are present in 26 per cent of football players with recurrent groin pain³⁵. Radiological hallmarks include non-specific irregularity of the cortical margin and pubic symphyseal widening (more than 7 mm). Erosions may occur leading to sclerosis at the pubic bone margins. Radiological assessment of the symphysis pubis in young men can be difficult, as ossification in that region varies considerably and findings may be misinterpreted²⁹. Subacute ischial avulsion may be mistaken for osteomyelitis or neoplasm^{36–39}. Radiography should be restricted to cases where there is clinical suspicion of a skeletal abnormality. An isotope bone scan using ^{99m}Tc may assist the diagnosis of osteitis pubis²⁵ but a negative scintigram does not exclude the diagnosis.

Management of osteitis pubis is difficult and frustrating⁴⁰. Debate continues between a conservative policy and surgical intervention. Conservative treatment involves aggressive physiotherapy to strengthen the hip rotators, flexors and adductors. Daily stretching should be encouraged, with avoidance of kicking and running, and sport should cease for 3–6 months¹. The use of intra-articular steroids has not been found to be useful^{20,34}. Surgery involving the pubic symphysis, leaving the anterior and posterior ligament intact, has been claimed to relieve the symptom of osteitis³⁴. Histological examination of local tissues shows only scattered fibrosis and chronic inflammation^{41,42}. The majority of patients respond to conservative

treatment and rehabilitation⁴³ but a successful return to full activity after treatment for osteitis pubis has been reported by some to be as low as 20 per cent¹⁷.

Stress fracture

Stress fracture is common in athletes, especially long distance runners. Pubic rami stress fractures accounted for 1.4–7.8 per cent of all stress fractures⁴⁴ and a South African study of 196 runners estimated that 10–15 per cent of pelvic stress fractures occur in women⁴⁵. Others have reported a higher incidence of pelvic stress fractures in women marathon runners, 72 per cent⁴⁶ to 79 per cent³⁰.

Pelvic stress fractures present with a gradual onset of groin and thigh pain⁴³ leading to inability to run for at least 8 weeks or more after the injury. Physical examination reveals tenderness to deep palpation over the pubic ramus. Athletes are unable to stand and support their full weight on the ipsilateral side⁴⁷. The diagnosis will be missed if the clinician is unaware of the significant number of stress fractures that are not radiologically apparent⁴⁸. Radiographs are often normal, especially early in the disease process; only 38 per cent of clinical pelvic stress fractures show radiologically⁴⁷. Bone scanning reveals increased uptake in the affected ramus⁴³ owing to increased blood flow and osteoblastic activity. A ^{99m}Tc bone scan is a sensitive method of identifying stress fracture and is appropriate when bony or pubic symphyseal tenderness is found on clinical examination. Diagnosis of stress fracture may be improved by a combination of radiography plus bone scintigraphy or repeated radiographic examination. When ^{99m}Tc scanning is combined with conventional radiography, the accuracy of diagnosis of stress fracture of the pubic bone is increased to 62 per cent²⁹.

Treatment of pubic stress fracture is rest for 4–6 weeks⁴⁵ and avoidance of pain-associated activity; delayed or non-union may occur if the athlete continues to run⁴⁶. Surgery is the treatment of choice in most cases of stress fracture of the femoral neck⁹. Avascular necrosis of the femoral head may also cause pain in the hip or groin. The main cause is trauma, resulting in a subcapital fracture. Fortunately, sports-related dislocation and displaced femoral neck fractures are rare, even in contact sports, but they may go unrecognized especially when there is no associated acetabular rim fracture⁴⁹.

Urological disease

Other common causes of obscure groin pain include prostatitis¹³, epididymitis, urethritis and hydrocele¹⁰. Prostatitis is probably the most frequently overlooked

condition. Rectal palpation and positive culture assist in the diagnosis and the treatment is with antibiotics, with or without non-steroidal anti-inflammatory agents⁵⁰.

Connective tissue disease

Although rare, the various connective tissue diseases, such as rheumatoid arthritis, should not be forgotten. Diseases such as gout, ankylosing spondylitis, Reiter's syndrome and other spondarthritides may also need to be investigated⁵¹.

Spinal and hip abnormalities

Early assessment of the spine and hip is required to identify sacrolumbar abnormalities and sinister lesions such as bone tumours. Old osteochondritis of the vertebral bodies, disc lesions at L1 or L2, and crush fractures can cause radicular pain and imitate groin strain. Boeda⁵² reported lower lumbar and sacral abnormalities responsible for excessive pelvic tilt and secondary stress in 16 athletes. H. Junge (unpublished results) reported a series of pelvic radiographs of 950 athletes that showed minor subluxation of the femoral head associated with groin pain and symphysis pubis lesions.

Nerve entrapment

There has been recent interest in neurogenic groin pain. Lovell *et al.*²⁵ have studied the clinical presentation of ilioinguinal neuralgia in a series of athletes with groin pain. Diagnosis involves finding tenderness in the region of the iliac fossa and injecting local anaesthetic at this site to relieve the pain²⁰. Obturator neuropathy has been described in a series of 32 patients⁵³. Diagnosis relies on exercise-induced medial thigh pain over the area of adductors, especially during kicking and twisting. There may be adductor muscle weakness as well as paraesthesia of the medial thigh after exercise and electromyography may demonstrate chronic denervation changes in the adductor muscles. Fascial entrapment of the obturator nerve is possible. Other nerve entrapments in the inguinal region include those of the genitofemoral⁵⁴ and ilioinguinal⁵⁵ nerves which cause local pain and neurological dysfunction. Nerve entrapment syndromes can be treated by exploration and surgical release of the nerve⁵³.

Investigations

High-performance athletes with severe pain or weakness often undergo imaging because their trainers and physicians perceive the need for accurate evaluation of the severity of injury to predict the period of convalescence and eventual

return to competition⁵⁶. Various imaging modalities are used to identify hernias and exclude other pathology. The peritoneal lining and hernial contents may be identified indirectly by herniography and directly visualized by ultrasonography, CT and MRI. There are limited reports on the sensitivity and specificity of CT and MRI for groin hernia, most of which are based on descriptions of appearances of various types of hernia^{57–60}. Laparoscopy is now also being evaluated in the investigation of sportsman's hernia.

Herniography

Herniography is performed by injecting contrast medium into the peritoneal cavity. The patient is then moved to an upright position and asked to strain. Anteroposterior and oblique views are taken. A number of reports have suggested the use of herniography to diagnose occult symptomatic groin hernia and to evaluate obscure groin and pelvic pain in adults^{4,23,61}. Herniography helps to identify the lesion and confirm that surgery may be warranted in the athlete with groin pain. Hernia has been found to be present in 19 (24 per cent) of 79 and 38 (36 per cent) of 106 cases of obscure groin pain in two separate studies using herniography^{62,63}. Smedberg *et al.* from Sweden, however, reported a much higher incidence. These authors first found that 51 per cent of men and 21 per cent of women with groin pain had impalpable but symptomatic hernia¹³; a second study reported an incidence of hernia of 84 per cent in elite athletes with groin pain¹¹. Herniography has been reported to have a high accuracy (95–99.5 per cent) and low false-negative rate (0.5–4.0 per cent) in the detection of abdominal wall hernia in other series^{64–66}. Lovell *et al.*²⁵, however, reported a lower sensitivity (82 per cent) and specificity (64 per cent), with a predictive value of 89 per cent; furthermore, negative herniography does not exclude an occult hernia. The complication (bowel puncture etc.) rate of herniography is 5–6 per cent^{61–67}.

Ultrasonography

Ultrasonography is a useful non-invasive adjunct to physical examination and is especially helpful in chronic injury. It provides valuable information such as the extent and location of tendinous injuries, demarcating partial tears as local hypoechoic areas with discontinuity of fibres within the fibrillary tendon tissue⁶⁸. Deitch and Soncrant⁶⁹ reported a sensitivity of 97 per cent with ultrasonography, in a series of 70 patients with ambiguous groin pain and questionable diagnosis. However, ultrasonography failed to diagnose two clinically obvious small indirect inguinal hernias. The limitation of the method relates to difficulty in

detecting occult hernias and a negative result does not exclude the diagnosis. Ultrasonography appears to be able to identify patients with a surgically remedial lesion, avoiding prolonged non-operative treatment as well as reducing the frequency of negative surgical exploration. The technique is not widely used in the USA but is more often used in Europe⁷.

Computed tomography

CT has established itself as the standard investigation in the evaluation of most soft tissue disease, especially soft tissue tumours and neuromuscular disease⁷⁰. However, its ability to identify abnormalities is limited by its fixed planes⁷¹. This can be overcome by employing helical CT scanning, which allows multiplanar reconstruction to be performed to permit better detection of hernias during straining. CT, by virtue of its supine scanning position, may fail to detect a reducible hernia⁷². The inferior epigastric vessels, an important landmark for direct and indirect inguinal hernia, cannot be identified clearly in all patients⁷¹.

CT has a more important role in the diagnosis of other pathological causes of chronic groin pain. With a spatial resolution of 1 mm and density resolution less than 0.5 per cent, it has become a standard method of soft tissue evaluation; for example, haematoma within injured muscle can be recognized with ease^{73–75}.

Magnetic resonance imaging

MRI is superior to CT for musculotendinous imaging because of its better soft tissue contrast, multiplanar capabilities (sagittal, coronal and oblique), lack of ionizing radiation and sensitivity for small lesions^{76–78}. MRI can clearly identify structures (inferior epigastric vessels, inguinal ligament, deep and superficial rings, inguinal canal, spermatic cord, round ligament and vascular structures) that are crucial in the assessment and differentiation of inguino-femoral hernias⁷¹. Van den Berg *et al.*⁷¹ reported a small prospective study of 13 patients in which 11 inguinal hernias were diagnosed correctly. There were no false positives.

MRI is also useful in the differential diagnosis of chronic groin pain. It can demonstrate damage to the conjoint tendon and outline the extent of muscular injury³³. Macroscopic injury, such as partial tear or complete rupture, can be identified as disruption of muscle and tendon fibres. Fluid accumulation and altered configuration of the muscle and tendon unit may be found. MRI is useful in excluding stress fractures²⁰ or avascular necrosis of the femoral head. It is superior to CT as an imaging modality for muscle strain injury except in circumstances of late

ectopic calcium deposition in injured muscle⁷⁹. MRI is of limited value in the diagnosis of calcified tendinitis and bony abnormality at tendon insertion points; these are better visualized using CT⁷⁹.

Despite superior soft tissue contrast, MRI has not been popular as a primary diagnostic imaging tool in the evaluation of groin hernia⁷¹. CT and MRI cannot be justified on grounds of cost for routine assessment of patients with groin pain but they may be performed in suspicious cases to define the anatomical extent of groin injury. The main advantage of ultrasonography, CT and MRI is their ability to identify conditions other than hernias that may be responsible for the symptoms. However, plain radiography, ultrasonography and scintigraphy should be considered as the first line of investigation to supplement clinical assessment. Herniography should be used in obscure chronic groin and pelvic pain or if a symptomatic occult groin hernia is suspected.

Laparoscopy

The role of laparoscopy in sportsman's hernia is still being evaluated. While it allows an opportunity to examine all the local hernial orifices^{80,81} and is more accurate than clinical diagnosis⁸⁰, it has a number of limitations. It does not permit an assessment of the anterior wall of the inguinal canal, notably the conjoint tendon, and commits the surgeon to a laparoscopic repair; it adds the risk of complications of laparoscopic surgery. Laparoscopy, however, may have a role in patients who have had multiple repairs.

Management

Conservative measures

Musculotendinous strain of the adductors and other muscle groups is the commonest cause of groin pain. Non-palpable inguinal hernia and subclinical abdominal defects without herniation are often overlooked. Diagnosis of groin pain is further complicated by the presence of multiple pathology²⁹. Many patients therefore undergo prolonged periods of physiotherapy with lengthy spells of rest and numerous radiological investigations before referral to the specialist. Initially, conservative management with rest, anti-inflammatory agents, stretching and strengthening exercise should be advised¹⁰. With such a conservative approach there is a gradual return to sports activity; it may be 3–6 months before full activity can be resumed.

Role of surgery

Opinions about the value of surgery differ greatly. Recent authors have advised modified herniorrhaphy^{8,12,15–18,82}.

Surgical intervention is contemplated when conservative management has failed. There is no consensus to support any particular surgical procedure.

Gilmore described the surgical restoration of the torn external oblique aponeurosis and conjoint tendon by modified herniorrhaphy, with plication of the transversalis fascia and polyglactin repair of the conjoint tendon. The latter is then approximated to the inguinal ligament with a nylon darn. The external oblique is repaired and the wound closed in layers¹². Others have approximated the torn edges of the external oblique with simple interrupted sutures rather than using the complex repair suggested by Gilmore. They also have reported good results with full sporting activity within 5–6 weeks in their small study⁸².

A number of different modified repairs of the posterior wall deficiency have been described. Malycha repairs the posterior inguinal wall in two layers; a continuous suture is inserted from the pubic tubercle to the internal ring followed by a second layer (with a loose darn over this layer). Smolaka¹⁴ reported that Nessoic (several hundred athletes) and Polglase *et al.*¹⁸ (64 patients) used the conventional Bassini repair for the weak posterior wall of the inguinal canal with success. Others suggest strengthening the inguinal ligament and transversalis fascia¹⁵, or closing the external ring and subcutaneous cord placement¹⁶. Hackney¹⁷ reported that Hyde tightens the conjoint tendon by reattaching the insertion of the tendon. Hyde claimed a 90 per cent success rate over 500 operations using this technique¹⁷. Hackney reported, in his series of 15 athletes, that 13 had returned to full activity and the remaining two were improved by repair¹⁷. Malycha and Lovell⁸ used a repair of the posterior inguinal wall, and 41 of 44 patients returned to normal preinjury activity; 75 per cent obtained good relief and 23 per cent obtained improvement of their initial symptoms. In cases of inguinal hernia, 63–70 per cent of athletes can expect cure from herniorrhaphy and a further 20–31 per cent will improve^{13,18}. Only 5 per cent have persistent groin pain and remain unhappy with the result of operation. Division or preservation of the ilioinguinal nerve does not affect the outcome in this respect¹⁸.

Conclusion

Groin pain continues to be an economic and personal burden in terms of absence from sport. It may result in chronic disability, leading to early retirement from competition due to delay or failure in treatment. Many symptoms will settle with conservative or non-operative measures but, despite 'negative' investigation, in severe and/or persistent cases surgical exploration is justified. Appropriate repair of the posterior wall of the inguinal canal has proven to be of

therapeutic benefit, offering cure to over 60 per cent of the patients and improvement to a further 20 per cent¹⁸.

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Exercise training and peripheral vascular disease

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Background: Conservative management is advocated as a treatment of choice for patients with intermittent claudication. This is a review of the mechanisms behind the improvement following an exercise rehabilitation programme.

Methods: All Medline articles from the National Library of Medicine, USA containing the text words 'claudication' or 'peripheral vascular disease' and 'exercise' were reviewed. Cross-referencing from relevant articles was carried out.

Results and conclusion: The poor physical status of a patient with intermittent claudication is not solely due to a reduction in blood flow to the lower limbs; associated factors, such as metabolic inefficiency, poor cardiorespiratory reserve and exercise-induced inflammation contribute. An exercise programme frequently improves both the physical aspect and quality of life, and the success of such exercise is multifactorial. An increase in the blood flow to the lower extremity is uncommon. Other factors, such as a redistribution of blood flow, changes in oxidative capacity of the skeletal muscles and greater utilization of oxygen, occur and the associated metabolic dysfunction of the skeletal muscles is rectified. Following exercise training, blood rheology improves and exercise-induced inflammation is ameliorated; cardiorespiratory status also benefits and the oxygen cost of exercise decreases.

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Introduction

Intermittent claudication is a common condition. Each year 2 per cent of the population under 60 years of age, rising to 5 per cent in the group over 70 years, are affected¹. Several studies have shown that 75 per cent of claudicants will remain stable or improve with time² and, as the overall amputation rate is low (4–8 per cent), symptomatically their prognosis is favourable³. The overall mortality rate, however, is 20–30 per cent at 5 years and 40–72 per cent at 10 years, three times greater than that of an age- and sex-matched population⁴. The commonest causes of death are myocardial infarction and cerebrovascular disease.

The mainstay of treatment for claudication is conservative therapy but improvement in percutaneous transluminal angioplasty techniques has resulted in a rapid rise in the numbers of these procedures. Tunis *et al.*⁵, in 1991, reported a 10-year study on the impact of angioplasty and vascular bypass in the management of peripheral arterial disease in Maryland, USA. Annual angioplasty rates increased from one to 24 per 100 000 population, while bypass surgery increased from 32 to 65 per 100 000. Interestingly, there was no decline in the overall rate of amputation (30 per 100 000).

The importance of conservative management for patients with intermittent claudication has since been re-emphasized⁶.

The original recommendation of an exercise programme as a method of treating patients with intermittent claudication came from Erb in 1898⁷. Foley⁸ reintroduced the concept in 1957 and Housley⁹ in 1988 summarized the management with his maxim 'Stop smoking and keep walking'. Currently there are reservations about enrolling diabetic claudicants into an exercise programme because of their poorer outlook compared with non-diabetics; more aggressive management is thought appropriate by some. Nevertheless, Lundgren *et al.*¹⁰ have shown that diabetics can improve their walking distance to a level similar to that of non-diabetic patients. Furthermore, in the light of current health economics it is inevitable that treatment costs will influence patient management. One of the advantages of an exercise programme is the cost: in 1994, the cost of angioplasty was US\$3636, compared with US\$114 for exercise training (twice a week for 2 h, duration 2 years)¹¹.

Many controlled trials have studied the effects of exercise training on patients with peripheral vascular disease. The few meta-analyses of these randomized studies have

generally agreed that the outcome (measured as walking distance) is good, the absolute walking distance regularly increasing by over 100 per cent¹²⁻¹⁴. The optimum programme should include risk factor management, and should be intensive, dynamic, supervised and of at least 2 months' duration; longer training periods yield greater benefit. Recent studies have compared the long-term results of angioplasty and exercise training^{15,16}; there is little difference at 5 years, with patients in the exercise group achieving a greater maximum walking distance over the first 15 months¹⁵. After 2 years there is no significant difference in the quality of life score (Nottingham Health Profile)¹⁶.

Outcome analysis of treatment programmes invariably uses maximum walking distance, measured on a treadmill, as the endpoint. Barletta *et al.*¹⁷, however, found a poor correlation between treadmill performance and quality of life scores (McMaster Health Index). A number of studies have demonstrated that a supervised exercise programme improves walking distance and functional status as determined by Walking Impairment Questionnaire, Physical Activity Recall, Medical Outcome Study SF-20 and -36, and Nottingham Health Profile¹⁸⁻²⁰. In contrast, Currie *et al.*²¹ demonstrated an improved quality of life score (SF-36) after angioplasty and/or surgery, but no significant improvement in an unsupervised exercise group.

Further work needs to be undertaken to clarify which patients are likely to benefit most from exercise and which from percutaneous transluminal angioplasty. There is good evidence that most claudicants with superficial femoral

artery disease benefit from conservative management, with some evidence that aortoiliac stenosis may be better treated by angioplasty¹⁵. However, there is little doubt that an exercise programme is an invaluable first-line treatment for the majority of patients as it is non-invasive, inexpensive, has minimal complications and produces a worthwhile improvement in walking distance. While the benefits of an exercise rehabilitation programme are recognized, the mechanisms involved are not completely appreciated. This is a review of current understanding of the factors leading to these benefits.

Blood flow

In one study the common femoral artery blood flow, measured at rest by a dye dilution technique, was 0.53 l/min in normal adults and 0.29 l/min in patients with claudication. During a standard exercise, this increased to 2.23 l/min in the normal controls, whereas flow increased to only 1.11 l/min in the claudicants²². This inability to increase lower limb blood flow results in exercise-induced pain, as the metabolic demands of the muscles exceed the body's ability to deliver the required substrate.

Exercise training improves maximum and pain-free walking distances in most patients. It has been suggested that this is due to an increase in the absolute blood flow, possibly secondary to the development of a collateral circulation. Initial studies on rats²³ and dogs²⁴ with ligated femoral arteries demonstrated that, following exercise training, the blood flow returned to preligation values

Table 1 Studies reporting changes in blood flow and walking distance

Reference	Year	n	Blood flow test	Walking distance (% increase)	Peripheral blood flow (% increase)	Duration of training (months)
Blumchen <i>et al.</i> ²⁶	1970	15	Venous occlusion plethysmography	—*	—*	6
Ericsson <i>et al.</i> ²⁷	1970	9	Venous occlusion plethysmography	97	45	11
Zetterquist ²⁸	1970	9	Venous occlusion plethysmography	73	n.s.	3-4
Fitzgerald <i>et al.</i> ²⁹	1971	19	Venous occlusion plethysmography	—	112	8-24
Dahlloff <i>et al.</i> ³⁰	1974	10	Venous occlusion plethysmography	116	n.s.	6
Ekroth <i>et al.</i> ³¹	1978	129	Venous occlusion plethysmography	150	n.s.	4-6
Lundgren <i>et al.</i> ³²	1989	25	Venous occlusion plethysmography	50	18	13
Mannarino <i>et al.</i> ³³	1989	8	Venous occlusion plethysmography	67	n.s.	6
Binaghi <i>et al.</i> ³⁴	1990	26	Venous occlusion plethysmography	82	n.s.	3
Hiatt <i>et al.</i> ³⁵	1990	9	Venous occlusion plethysmography	117	38	3
Mannarino <i>et al.</i> ³⁶	1991	10	Venous occlusion plethysmography	86	n.s.	6
Pancera <i>et al.</i> ³⁷	1995	15	Venous occlusion plethysmography	58	n.s.	1
Johnson <i>et al.</i> ³⁸	1989	10	Duplex ultrasonography	42	n.s.	5
Larsen and Lassen ³⁹	1966	7	Xenon-133 clearance	325	n.s.	6
Alpert <i>et al.</i> ⁴⁰	1969	19	Xenon-133 clearance	74	6	6
Sorlie and Myhre ⁴¹	1978	10	Thermodilution	79	n.s.	3-4

*Percentage change was not stated; walking distance was 325 m and peripheral blood flow was 3.28 ml per min per 100 g. n.s., Change not significant

within a year²⁵. However, in patients with intermittent claudication, most studies have shown little or no increase (Table 1)^{26–41}. Work using venous occlusion plethysmography has demonstrated in respect of blood flow after an otherwise successful exercise programme^{26–37}. Johnson *et al.*³⁸ used a duplex scanner to demonstrate that in claudicants the common femoral artery blood flow remains similar to pre-exercise levels despite a maximum walking distance increase of over 40 per cent after exercise. Similar results were reported by Sorlie and Myhre⁴¹ who used a thermodilution technique to measure blood flow.

Alpert *et al.*⁴⁰ found that the clearance rate of xenon-133 injected into the calf muscles of claudicants increased after exercise training. Since most studies do not show any increase in blood flow, these authors proposed the concept of a redistribution of blood with training. They hypothesized that there was a diversion of blood from minimally active muscles (low oxygen extraction rate) to exercising muscles (high oxygen extraction rate). This idea was supported by a study showing reduced femoral venous oxygen saturation during exercise in claudicants after an exercise training programme^{28,41}. However, the increased lower limb oxygen uptake may not be due simply to a redistribution of blood flow to more active muscles as the metabolic capabilities of muscle fibres change after exercise training.

Gardner and Poehlman¹⁴ reviewed studies of exercise training for claudicants and concluded that the increase in lower limb blood flow was small while exercise tolerance regularly increased by over 100 per cent. The Pearson correlation between the improvement in blood flow and walking distance lies between 0.23 and 0.55, indicating that the flow increase could account for only 5–30 per cent of the improvement in walking distance. Therefore current evidence does not support the hypothesis that an improvement in blood flow is the main factor leading to an increase in exercise tolerance. This view is reinforced by the finding of no or poor correlation between lower limb blood flow and walking distance. Furthermore, exercise-trained patients have a better exercise tolerance than those who have had angioplasty (which would presumably increase blood flow)^{15,16}. Therefore, an improvement in blood flow is not a prerequisite for a successful exercise programme.

Muscle metabolism: an introduction

The mechanical function of skeletal muscle is absolutely dependent on a continuous supply of fuel for the synthesis of adenosine 5'-triphosphate (ATP) which serves as an immediately available form of energy. Although the ATP stored in muscle is sufficient for only a short period of activity, much larger amounts of energy are stored as

creatine phosphate, which can be rapidly converted to ATP. Aerobic synthesis of ATP in mitochondria is the most efficient method of producing this substrate and the major fuel for this process is glucose and fatty acids. If the oxygen supply is limited, anaerobic metabolism ensues in which pyruvate is converted to lactic acid rather than acetyl-CoA. This bypasses the citric acid cycle and consequently generates only small amounts of ATP (2 *versus* 38 mol per mol glucose).

During resting or light exercise skeletal muscles utilize fatty acids (β -oxidation) as the main source of energy. These can only be used by the oxidative processes in the mitochondria. Increasing the exercise intensity leads to glycolysis of carbohydrate. Compared with glucose, fatty acid oxidation generates more ATP, but at a higher oxygen cost. A six-carbon fatty acid provides 44 mol of ATP (compared with 38 mol for glucose), but requires 8 mol of oxygen (6 mol for glucose). Therefore the respiratory quotient of glucose is 1 and for a six-carbon fatty acid is 0.75. Adaptation after endurance training is manifested by the ability to utilize fatty acids more effectively, as demonstrated by trained athletes.

In patients with peripheral vascular disease, increasing the workload causes an inequality in the supply of and demand for oxygen. Aerobic generation of ATP becomes inadequate and anaerobic metabolism predominates. The result is an increase in lactic acid production, and a depletion of ATP and creatine phosphate, leading to pain²². Compared with normal subjects, the recovery of high-energy phosphate substrate in the muscles is slower⁴² and so patients with peripheral arterial disease have both a poor physical tolerance of exercise and a prolonged recovery time.

Morphological and biochemical changes associated with chronic occlusive disease

Skeletal muscles are divided into two types, I and II (Table 2). Patients with critical ischaemia have widespread

Table 2 Classification of fibre types in skeletal muscle

Features	Type I	Type II
Colour	Red	White
Contractility	Slow twitch	Fast twitch
Function	Postural	Fine movement
Mitochondria density	High	Low
Oxidative capacity	High	Low
Glycolytic capacity	Low	High
Enzymes	Citrate synthase Succinate dehydrogenase Cytochrome oxidase	Lactate dehydrogenase Pyruvate kinase

destruction of muscle fibres and replacement with connective tissue⁴³. Those with less severe disease demonstrate a more varied picture, ranging from selective loss of type II fibres⁴⁴ to no loss of fibres⁴⁵, or an increase in the number of type I fibres⁴⁶. Some studies have shown selective loss of type IIB fibres (which have a lower aerobic/oxidative potential than type IIA)⁴⁷. It is uncertain whether this varied picture reflects either the different degrees of severity of the disease or the level of physical activity of the patients.

Muscles are not the only specialized cells affected by chronic ischaemia; the peripheral nervous system is also susceptible to hypoxia. In most patients with mild to moderate disease, changes due to denervation and re-nerivation are seen in both motor and sensory nerves, and this occurs even in non-diabetic patients^{48–50}. Eames and Lange⁵¹ reported that 88 per cent of claudicants have sensory impairment and 56 per cent have motor weakness, which has a detrimental effect on the biomechanics of walking⁴⁴. Denervation injury is confirmed by histological findings of angular muscle fibres and an abnormal motor unit action potential in electromyography studies⁵².

Analysis of muscle enzyme activities in claudicants produces a heterogeneous result. A number of studies have shown an increase in oxidative enzymes (citrate synthase and cytochrome oxidase) in the calf muscles of patients with peripheral vascular disease^{46,53,54} which is reversed following vascular bypass procedures¹⁰. In animal studies, hypoxia *per se* does not induce an increase in the metabolic capacity of muscles; a combination of hypoxia and physical activity is required to stimulate enzyme production. In fact, claudicants who exercise infrequently may develop histological and biochemical features similar to those seen in athletes who stop training^{55–58}. Classically the deconditioning effect has characteristic features including loss of muscle fibres and a fall in mitochondrial oxidative enzyme levels. These low oxidative enzyme activities are associated with limited exercise tolerance and correlate with the clinical severity of the disease⁵⁴.

Investigation utilizing electron microscopy has identified structural abnormalities in lower limb muscle mitochondria of patients with intermittent claudication⁵⁹. As most oxidative and respiratory chain metabolism occurs in the mitochondria, such abnormalities may affect the metabolic function of the muscles. Nuclear magnetic resonance (NMR) spectroscopy has demonstrated that the requirement for ATP in claudicants is twice as high as in normal controls for a standard workload⁶⁰. This metabolic inefficiency is supported by the finding of an accumulation of acylcarnitine in patients with claudication^{61,62}. This substrate is an intermediate metabolite in the pathway of oxidative metabolism. Transportation of fatty acids into the

mitochondria requires conjugation with carnitine, the complex then shuttling across the membrane by a translocase. Accumulation of acylcarnitine is a marker of disturbance of the oxidative pathway. Claudicants, exercising to their maximum walking distance, double the concentration of short-chain acylcarnitine in the muscles of the symptomatic limb; this does not occur in the asymptomatic leg. In addition, the level of muscle short-chain acylcarnitine at rest inversely correlates with peak exercise performance ($r = -0.75$, $P < 0.05$)⁶². Although the mechanism behind the metabolic dysfunction is not fully understood, therapeutic manipulation with oral supplementation of propionyl-L-carnitine leads to a significant improvement in the walking distance of claudicants (by 46 per cent in placebo *versus* 73 per cent in the supplemented group after 24 weeks)⁶³.

So the adaptive response of skeletal muscles in patients with peripheral vascular disease is variable. The changes vary from minimal alteration to selective loss of muscle fibres (type I or II), or generalized atrophy. Denervation of the skeletal muscles is common. While there is evidence of an increase in the concentration of enzymes involved in the oxidative process, this does not signify a more metabolically efficient muscle. Indeed metabolic dysfunction is suspected, with a resultant impairment of muscle performance and poor exercise tolerance.

Effects of exercise training on muscles and metabolism

Exercise training leads to numerous changes in muscle structure and function in normal subjects. There is an increase in the number of mitochondria per muscle fibre, a higher level of oxidative enzymes, a slower utilization of muscle glycogen and blood glucose, and a greater reliance on fatty acid oxidation^{64–67}. The respiratory exchange ratio (carbon dioxide production : oxygen utilization) diminishes as a result of the increase in fatty acid oxidation.

Similar changes occur after a period of exercise training in patients with peripheral vascular disease. For a similar workload, femoral venous blood from claudicants who complete an exercise programme has a lower lactic acid concentration than was recorded before training^{68–71} and there is an increase in the arteriovenous oxygen difference^{28,39}. NMR spectroscopy after exercise training demonstrates a reduction in the level of lactic acid and less phosphocreatinine depletion under a similar workload⁷² (phosphocreatinine depletion is a measurement of energy utilized for exercise). These changes indicate greater ATP production, less reliance on anaerobic metabolism and hence an improvement in muscle energy state.

Enzymatic changes associated with training have been studied by muscle biopsies before and after an exercise training programme. Significant increases in the levels of oxidative enzymes such as cytochrome oxidase and succinic oxidase have been reported, with a small rise in citrate synthase^{10,73}. Patients with a low level of cytochrome oxidase (compared with normal) before training have a markedly improved level on completion of an exercise programme¹⁰. The low enzyme activity before training may result from reduced physical activity, muscle fibre depletion or mitochondrial damage secondary to ischaemia. Therefore, exercise training may reverse the low oxidative capacity of the muscles.

In claudicants, the respiratory exchange ratio for a given workload decreases after training³⁵. This is similar to the response of normal individuals and represents an enhancement of fatty acid oxidation. As explained above, fatty acids can only be metabolized aerobically in the mitochondria to produce ATP. This suggests greater oxidative capability, either by an increase in mitochondrial function (as measured by oxidative enzyme activities) or by better oxygen delivery. Exercise training does not alter the anaerobic capacity, as proven by a constant level of lactate dehydrogenase¹⁰.

Acylcarnitine is a marker of metabolic dysfunction and is linked to the limitation in physical tolerance of patients with peripheral arterial disease. After exercise training, a reduction in plasma acylcarnitine level correlates with an increase in maximum walking distance³⁵. Patients who achieve a higher peak oxygen uptake following an exercise programme have a greater reduction in muscle acylcarnitine level than those who do not improve their oxygen uptake⁵⁰.

Exercise training may not be entirely beneficial. Denervation of skeletal muscles is common in patients with peripheral vascular disease and exercise aggravates this condition. Denervation injury may affect both the mechanics of muscular contraction and oxidative enzyme activity⁵⁰. Fortunately the denervation injury does not prevent the improvement in exercise tolerance of patients after training; the long-term effect is still unknown.

In summary, exercise training improves the physical tolerance of patients with claudication. The muscles adapt by improving their aerobic metabolism leading to greater utilization of oxygen. Less reliance on anaerobic metabolism reduces lactic acid production and improves the muscle energy, thereby helping to rectify the associated metabolic dysfunction.

Exercise-induced inflammation

Ischaemia leads to inflammation⁷⁴. Claudicants have repeated cycles of exercise-induced pain followed by a recovery phase. They are therefore subjected to multiple

episodes of low-grade inflammation. Indeed, the recovery or resting phase may promote an inflammation that is more severe than the initial insult, a process of reperfusion injury⁷⁵. It is not clear whether reperfusion injury is a distinct entity or simply a progression of ischaemic injury and the initiating factors of reperfusion injury are poorly understood. Nevertheless, it is clear from many studies that exercise to the limit of pain leads to activation of the inflammation cascade.

Exercise in claudicants induces a higher neutrophil count (more of which are activated) in the femoral vein of the symptomatic limb than that of the asymptomatic limb⁷⁶. Neutrophil activation results in the release of inflammatory proteins^{77,78}, such as thromboxane A₂ and leukotrienes, promoting aggregation and activation of platelets⁷⁹ and neutrophils, thereby increasing vascular permeability⁸⁰ and vasoconstriction. Neutrophils also release proteases such as elastase, leading to endothelial damage⁸¹. There is activation of complement factors, which act as chemotactic factors or cause direct damage to the endothelium. Physical obstruction of the microvascular circulation occurs because of adhesion of activated neutrophils to the endothelium⁸². Another form of insult is the generation of oxygen free radicals, highly unstable and reactive molecules. The source of these may be the xanthine pathway during the reperfusion phase⁸³; they may be released by the activated neutrophils or even leaked from the electron transport chain in the mitochondria⁸⁴. The free radicals may damage the endothelium of the arteries, promoting activation of leucocytes and activating membrane phospholipase, leading to synthesis of eicosanoids (prostaglandin, leukotrienes and thromboxane)⁸⁵. The damaging effect of the free radicals is neutralized by the antioxidant defence system, involving superoxide dismutase, catalase, glutathione peroxidase and vitamins C and E. Perhaps not surprisingly, the level of antioxidants falls in exercising claudicants because they are used to neutralize free radicals⁸⁶.

The inflammatory reaction is not limited locally. Its systemic effect is illustrated by an increased endothelial permeability in the glomeruli of patients with peripheral vascular disease which leads to microalbuminuria⁸⁷. The loss of albumin is accentuated by exercise, an occurrence that does not happen in normal controls⁸⁸. This feature may be reversed by both bypass surgery^{89,90} and angioplasty⁹¹.

Effects of exercise training on blood rheology and exercise-induced inflammation

Exercise-trained patients have an attenuation of the postexercise albumin excretion that is not seen in controls⁸⁸. This response is similar to that in claudicants who have undergone vascular bypass. Levels of stable biochemical

markers (C-reactive protein (CRP) and serum amyloid A protein) are also reduced following a 6-month exercise programme⁸⁸. Ernst and Matrai⁹² documented the effect of exercise training in relation to peak walking distance, plasma and blood viscosity, blood cell filterability and red cell aggregation. After 2 months of exercise, the plasma and blood viscosities return to normal values, blood cell filterability rises and red cell aggregation decreases⁹³. These results contrast with those of Ciuffetti *et al.*⁹⁴ who demonstrated no significant changes. The desirable effect of physical training in increasing the fluidity of the blood also occurs in a healthy sedentary population⁹⁵, but the mechanism behind this is unknown. Physical training leads to an increase in plasma volume⁹⁶, leading to a decrease in haematocrit, which may be a factor in the reduction of blood viscosity⁹⁷. Even though the haematocrit did not change in Ernst and Matrai's study⁹², it has been shown previously that altering the haematocrit of patients with peripheral vascular disease to about 40 per cent by venesection improves lower limb blood flow significantly⁹⁸.

Exercise training is not the only factor that alters the inflammatory response during exercise. Studies in coronary artery disease have shown that smoking increases CRP levels⁹⁹ while aspirin reduces both cytokine and CRP levels¹⁰⁰. Recently, the Cholesterol and Recurrent Events study has shown that treatment with pravastatin leads to significant reductions in CRP levels, but these reductions do not correlate with lipid levels¹⁰¹. It is likely that additional medical treatments and lifestyle management of claudicants significantly influence the levels of inflammatory markers.

Short periods of submaximal ischaemia offer protection from prolonged ischaemia to myocardial muscle. The term 'ischaemic preconditioning' was coined when it was noticed that the size of myocardial infarct was smaller if the heart muscle was preconditioned by submaximal ischaemia. A few episodes of brief, non-lethal ischaemia before a potentially fatal ischaemic event protect the myocardial muscle. This paradoxical phenomenon has been studied in many animal models^{102–105}. The mechanisms are still unknown but a few important observations have been noted. The preconditioned muscle has a slower rate of ATP depletion in subsequent ischaemic attacks. Additionally, harmful by-product accumulation is reduced owing to the reperfusion or washout cycle. Recently, the role of adenosine has been highlighted^{106,107}. It has a cellular protecting property and depresses platelet and leucocyte activation. The possibility that exercise training in patients with peripheral arterial disease produces a similar biological response to myocardial preconditioning has been investigated by Capecchi *et al.*¹⁰⁷. Patients were 'preconditioned' by performing submaximal treadmill exercise which led to a significant improvement in

maximum walking distance, whole-blood filterability and blood viscosity. As expected, the adenosine level was higher than resting level after each treadmill exercise, presumably to protect cells from ischaemia-reperfusion injury. More importantly, the increase in level of adenosine (for a similar workload) was less after a period of training. The authors suggested that the lower adenosine level could represent a reduced requirement for this cell protective substrate, or a lower level of ischaemia after exposure to submaximal exercise.

In summary, exercise to the limit of claudication leads to a local and systemic inflammatory response. Concerns that exercise training leads to progression of atherosclerosis from inflammation are misplaced. Such training causes attenuation of inflammation and improves blood rheological properties. Furthermore, the effect of training may be analogous to the biological response associated with myocardial ischaemic preconditioning.

Effects of training on cardiorespiratory system and biomechanics of walking

Compared with normal subjects, patients with intermittent claudication have a lower maximum oxygen utilization but have a higher oxygen utilization when they are walking¹⁰⁸. Patients with atherosclerosis (ischaemic heart disease and peripheral arterial disease) may respond to an exercise rehabilitation programme by showing a decrease in steady-state oxygen utilization during treadmill testing^{71,109}. This reduction implies that the oxygen cost for the same workload has decreased. As most patients with peripheral arterial disease are smokers and likely to have reduced respiratory function¹¹⁰, the reduction in oxygen cost may be an important factor leading to an improvement in physical tolerance. Reduction of oxygen cost may also be due to an improvement in the biomechanics of walking¹¹¹. Animal models have proven that ischaemic pain can lead to gait disturbance¹¹² and, following exercise training, normal elderly subjects have a significant improvement in gait pattern¹¹³. Part of the benefit of exercise training is an improvement in cardiac status, demonstrated by a lower resting and exercising heart rate, which improves myocardial oxygenation and function¹¹⁴.

In summary, exercise training leads to a reduction in oxygen cost of exercise, a higher peak oxygen utilization and a reduction in heart rate. This represents an improvement in the cardiorespiratory status of the patient.

Psychology

Exercise rehabilitation improves the functional well being of patients with peripheral vascular disease. Most appreciate

and welcome the additional attention of an exercise programme. In 1990, Rosfors *et al.*¹¹⁵ identified a few important predictors of outcome. The best correlation with good outcome is belief that exercise will lead to an improvement in walking status. Other less significant factors are the number of years the patient has been smoking and the initial (pretraining) walking distance. These authors suggest that cognitive factors are important in the outcome of an exercise programme. The possibility of endorphin release with training has been suggested, but no studies have yet been performed on claudicants. Unfortunately, many patients in exercise programmes leave after a few years¹⁵.

Conclusion

Exercise training should be the cornerstone of treatment for most claudicants; a significant improvement in walking performance can be expected. A multitude of physiological changes occur with training. Of particular benefit are improvements in cardiorespiratory status, blood rheology, muscle metabolism and biomechanical status. A period of physical training attenuates the inflammatory response associated with exercise in claudicants.

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Professor Seiki Matsuno, Chief Editor of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the July to September 1999 issues of the journal for this quarter's digest. A digest of *BJS* for the same period written by Professor Pierre Guillou, Associate Editor, appears in the Japanese journal.

Oesophagus

The results of surgical treatment for advanced oesophageal cancer remain extremely poor¹. Irradiation and chemotherapy are not superior to surgery. Perioperative morbidity and the influence on long-term survival of a combination of surgery and preoperative chemotherapy were investigated in patients with advanced oesophageal cancer. Forty-nine patients with advanced oesophageal squamous cell carcinoma were subjected to preoperative chemotherapy with cisplatin-5-fluorouracil. Fifty-seven patients were chosen as a historical control group who had not undergone chemotherapy before operation but had the same histological stages as those in the chemotherapy group. The response to chemotherapy was assessed by histological examination of surgical specimens. The survival rates showed no significant difference between preoperative chemotherapy plus surgery and resection alone. However, subclassification according to the grading of chemotherapeutic effectiveness showed that, compared with controls, preoperative chemotherapy was beneficial in high responders ($P=0.01$), ineffective in low responders ($P=0.61$) and detrimental in non-responders ($P=0.03$). Postoperative morbidity was significantly higher in the chemotherapy group than in controls ($P=0.02$). These findings suggest that preoperative chemotherapy is necessary only for high responders and therefore it is crucial to identify non-responders, low and high responders reliably before chemotherapy to improve the survival and quality of life of patients with advanced oesophageal cancer.

Stomach

There were two reports on the treatment of patients with gastric cancer over 80 years of age. Treatment strategies in such patients have not yet been well defined². The authors examined the incidence of postoperative complications and hospital mortality with respect to the preoperative condition of such patients. Preoperative examination included evaluation of cardiac, pulmonary, renal and hepatic function, the presence or absence of anaemia, nutritional status and blood sugar content. The incidence of postoperative complications and hospital mortality was studied in relation to the number of abnormal preoperative variables. The incidence of postoperative complications was 37.0 per cent. The hospital mortality rate was 11.1 per cent. Among patients

with abnormalities in five or more items, the incidence of complications was 76.9 per cent and the rate of hospital deaths was 23.1 per cent. For patients with an operating time of 4 h or longer, the incidence of complications was 71.4 per cent. In patients who underwent a curative resection the 5-year survival rate was 92.3 per cent. For elderly patients with gastric cancer and abnormalities in five or more items on preoperative examination, and for those showing a poor level of daily life activity, a less invasive treatment modality should be planned. Patients with abnormalities of four or fewer items at preoperative examination appear to be good candidates for curative resection.

Another study was undertaken to determine the most appropriate form of operation for elderly patients with gastric cancer in relation to postoperative complications and long-term survival³. A total of 72 consecutive patients over 80 years of age who underwent partial or total gastrectomy were evaluated using an E-PASS scoring system. This system comprises a preoperative risk score (PRS), a surgical stress score (SSS) and a comprehensive risk score (CRS), determined by both the PRS and SSS. Patients with a CRS of 0.5 or more had significantly higher rates of morbidity and mortality (45.0 and 20.0 per cent respectively) than those with a CRS of 0.5 or less (17.0 and 2.1 per cent). A Cox regression analysis of long-term survival, including death from other causes, identified five significant prognostic factors: stage, curability, SSS, CRS and allogeneic blood transfusion. In patients with no apparent residual cancer, a significantly better survival rate was noted in those who underwent less invasive surgery (SSS of less than 0.25), those with a CRS of 0.5 or less, and those who had not been given a blood transfusion. These results suggest that less invasive surgery not requiring a blood transfusion is advisable for patients aged over 80 years with gastric cancer. Furthermore, gastrectomy in patients with a CRS of 0.5 or more may have a poor therapeutic effect on both early and long-term outcome.

Colon and rectum

The purpose of this study was to compare the functional outcomes of colonic J pouch anastomosis at low anterior resection (J-LAR) for lower rectal cancer with those of traditional straight anastomosis (S-LAR)⁴. A questionnaire regarding anorectal function was used 1 year after operation for patients who underwent J-LAR ($n=15$) and S-LAR

($n = 30$). Clinical function was assessed by an incontinence scoring system. Physiological function was assessed by anorectal manometry and the balloon expulsion test. No patient had a diverting stoma. Median bowel frequency 1 year after operation was 4.8 (range 3–6) in the S-LAR group and decreased significantly to 1.8 (1–3) in the J-LAR group ($P < 0.05$). Complete evacuation was 50 (range 40–60) per cent in the S-LAR group and increased significantly to 81 (60–90) per cent in the J-LAR group ($P < 0.05$). Neorectal compliance was 2.2 (1.4–2.9) ml/mmHg in the S-LAR group and increased significantly to 3.1 (1.3–3.5) ml/mmHg in the J-LAR group ($P < 0.01$). No significant difference was observed between the two groups with respect to maximum resting or maximum voluntary squeeze pressure. The authors concluded that colonic pouch anastomosis performed after a low anterior resection to support the compliance of the (neo)rectum is an important factor in retaining a satisfactory bowel frequency.

The next study was designed to investigate the significance of p53 and bcl-2 expression in metachronous colorectal adenomas arising in the remaining colon after carcinoma resection⁵. The authors analysed p53 and bcl-2 expression immunohistochemically in initial adenomas (type I), synchronous adenomas with concurrent carcinoma (type II) and metachronous adenomas arising after resection of initial adenomas (type III) and carcinoma (type IV). The incidence of p53 immunoreactivity in type IV adenomas with mild dysplasia was significantly higher than that in type I, II or III adenomas with mild dysplasia. Bcl-2 immunoreactivity was more frequently detected in type IV adenomas with mild dysplasia than in type I or III adenomas with mild dysplasia. Coexpression of p53 and bcl-2 was detected in 16 per cent of type IV adenomas, a significantly higher frequency than that seen in type I, II or III adenomas. These results suggest that the evaluation of p53 and bcl-2 in metachronous adenomas in the remaining colon after resection of carcinoma may be a useful biological marker for assessing the risk of cancer development.

Liver and pancreas

The significance of p53 mutations in the primary lesion for recurrent hepatocellular carcinoma (HCC) was evaluated⁶. Mutations of p53 were examined using non-radioisotopic polymerase chain reaction single-strand conformation polymorphism in 98 resected HCCs. Of the 98 cases, 25 (26 per cent) had a p53 mutation. In 83 patients who survived surgery, the presence of a p53 mutation was associated with a shortened overall survival time ($P < 0.001$) and a shortened cancer-free survival time ($P < 0.05$). In 43 patients who developed recurrence there was no statistically significant correlation between the status of p53 in the

primary lesion and the clinical features of recurrent HCCs examined (i.e. extrahepatic metastasis, the number and extent of recurrent tumours, and treatment of recurrent tumours). However, the survival rate after recurrence was significantly lower in patients in whom a p53 mutation had been detected in the primary lesion ($P < 0.01$). A multivariate analysis for prognostic value after recurrence revealed that the p53 mutation was a useful independent prognostic factor affecting survival after recurrence ($P < 0.01$). In conclusion, the findings suggest that HCCs with p53 mutations have a high malignant potential based on their poor prognosis. Therefore a p53 mutation in the primary lesion is useful as an indicator of the biological behaviour of recurrent HCC.

Lung

The intrapulmonary thrombi that form after the cessation of circulation are thought to be one of the major causes of functional graft failure⁷. The authors evaluated the effect of recombinant tissue-type plasminogen activator (rtPA) in a canine cadaver lung transplant model. Donor dogs were killed by the intravenous administration of pancuronium bromide without heparinization and left for 2 h at room temperature. The donor lungs were then flushed with a low-potassium dextran glucose solution, being subjected to a total ischaemic time of 3 h. After left lung transplantation, the contralateral pulmonary artery of the recipient dog was ligated. In group 1 ($n = 6$) chloride solution was administered from the main pulmonary artery for 90 min, commencing 15 min before reperfusion. In group 2 ($n = 6$) rtPA 2.5 µg/kg per min, and in group 3 ($n = 6$) rtPA 5.0 µg/kg per min, was infused continuously in the same manner as in group 1. Lung function, including arterial blood gases and pulmonary haemodynamics, was measured for 3 h. The side-effects of rtPA were evaluated by measuring the prothrombin time (PT), activated partial thromboplastin time (APTT) and levels of fibrinogen, α_2 -plasmin inhibitor, plasminogen and fibrin-fibrinogen degradation product (FDP). All of the animals in the three groups survived throughout the observation period. Group 3 animals had significantly better gas exchange than those in group 1, and pulmonary haemodynamics were significantly better in group 2 and 3 animals than in group 1. The FDP levels in group 2 and 3 animals were significantly higher than those in group 1 animals, while the PT and APTT were significantly prolonged in group 3. These findings suggest that rtPA improves early lung function, particularly pulmonary haemodynamics.

Other authors recently developed an intrathoracic light-assisted anterior limited thoracotomy (LLAAL/T) for use in lung cancer surgery⁸. A skin incision 12 cm long is made

below the breast, the pectoral major muscle is divided and the fourth intercostal space is opened with a disconnection of the anterior cartilagenous portion. The posterior skin, including the serratus anterior muscle, is drawn posteriorly with a retractor. To illuminate the posterior and apical portions of the thoracic cavity, a flexible-fibre light is introduced into the thorax through the eighth intercostal space at the posterior axillary line. These techniques provide adequate exposure and sufficient illumination in the thoracic cavity, thus making surgery easy for most thoracic applications. Using this approach, 28 lung resections with a mediastinal nodal dissection for lung cancer (24 lobectomies, two bilobectomies and two pneumonectomies) were carried out without difficulty. The mean intrasurgical blood loss was 217 ml and the mean operating time 262 min; the duration of chest tube drainage was 2-3 days. Only one patient required a blood transfusion. All patients underwent continuous epidural anaesthesia until postoperative day 8. Other analgesic medication was required a mean of 0.5 times per patient until day 13, but none was needed from day 14 onwards. The authors concluded that ILAALT is a low-invasive thoracotomy, indicated for most types of lung cancer surgery, providing a reduction of pain as its main advantage.

Cardiac surgery

The effects of changing the calcium content of a continuous warm hyperkalaemic crystalloid cardioplegia (CWCP) were investigated in an isolated rat heart preparation⁹. The hearts were divided into eight groups of six each. A control group consisted of fresh non-arrested hearts and the remaining seven groups consisted of hearts perfused with continuous hyperkalaemic (20 mmol/l) modified Krebs-Henseleit bicarbonate buffer solution with calcium concentrations of 0.1, 0.3, 0.5, 1.0, 1.5, 2.0 or 2.5 mmol/l for either 180 or 240 min at 37°C. In the hearts arrested for 180 min, there were no significant differences in postarrest cardiac function between the control group and any of the groups perfused with calcium concentrations of 0.5 mmol/l or more. With a calcium concentration of 0.1 mmol/l, the calcium paradox was provoked. The change in the calcium content of CWCP perfused for 240 min significantly affected myocardial protection. Mean(s.e.m.) maximum aortic flow recovery of 74.7(2.7) per cent and minimum creatine kinase release of 15.7(2.4) units per 15 min per g dry weight were observed in hearts perfused with a calcium concentration of 1.5 mmol/l. The calcium paradox occurred even at a calcium concentration of 0.3 mmol/l. The authors concluded that normal calcium concentrations should be maintained in cardiac surgery to prevent cardiac injury.

A further study was designed to determine the effect of reperfusion of donor hearts in a perfusion apparatus after 60 min of global ischaemia before heart transplantation¹⁰. Thirteen dogs were exsanguinated from the femoral artery and cardiac arrest was achieved. The hearts were left *in situ* at room temperature (25°C) for 60 min. In group A ($n=7$) the hearts were excised and reperfused 60 min after cardiac arrest in the perfusion apparatus with substrate-enriched warm blood cardioplegia (WBCP) containing a hydroxyl radical scavenger, enzyme-product complex, followed by 45 min of blood perfusion. Next, the hearts were preserved in cold (4°C) University of Wisconsin (UW) solution. In group B ($n=6$) the hearts were perfused with cold (4°C) St Thomas' solution 60 min after cardiac arrest and preserved in cold UW solution. Thereafter, all hearts in both groups were transplanted orthotopically to recipient dogs. In group A six of seven dogs were weaned from cardiopulmonary bypass. In group B only two of six dogs were weaned from bypass. Moreover, three of the six hearts in group B did not start beating after transplantation (stone heart). This study suggests that reperfusion of the donor heart in the perfusion apparatus with WBCP is a beneficial preconditioning method when utilizing 60-min arrested hearts for transplantation.

General surgery

The effects of intraperitoneal 5-fluorouracil (5-FU), cisplatin, doxorubicin and methotrexate administration on rat intestinal anastomosis were compared¹¹. Cisplatin and methotrexate led to significant weight loss in the first 5 days compared with the control group. Within 14 days all rats except those in the methotrexate group nearly reached their preoperative weight. No remarkable weight loss or systemic toxicity was observed among the 5-FU and doxorubicin groups. The anastomotic bursting pressure at 1 week was significantly lower than that of the control group ($P<0.01$ and $P<0.005$ respectively). On day 14 the anastomotic bursting pressure in the cisplatin group was similar to that of the control group, but was significantly lower in the methotrexate group ($P<0.002$). Histopathologically, methotrexate avoided the development of a mucosal layer at the anastomosis site and led to ulcer formation in some of the rats. The bursting pressures at 7 and 14 days were similar to those in the control group. None of the agents had any significant mechanical or adverse histopathological effects on the anastomosis. These findings suggest that methotrexate impaired the healing of the anastomosis, and the authors concluded that the intraperitoneal administration of this agent is not safe. On the other hand, cisplatin had a detrimental effect on the

anastomosis, particularly in the early phase, but this effect disappeared in the late phase. Therefore cisplatin should not be administered in the early postoperative phase. As a result, 5-FU and doxorubicin were found to be the safest agents as they did not delay wound healing and did not reduce the anastomotic strength.

There were two reports on postoperative infections. A bacteriological study of 108 patients undergoing gastro-intestinal surgery was conducted by analysing intra-abdominal bacterial contamination (IABC) and postoperative surgical site infection (SSI)¹². The authors utilized an anaerobic porter to detect intra-abdominal bacterial infection and transport bacteria to the laboratory. The positive IABC rate was 42.9 per cent for gastric cancer surgery, 22.6 per cent for biliary tract surgery and 85.7 per cent for colorectal cancer surgery. Most cases of SSI were IABC positive, and isolated bacterial species from the SSI were similar to those from the IABC. In colorectal cancer surgery, a preoperative chemical intestinal preparation and the prophylactic use of antibiotics had a major influence on the sensitivity of bacteria isolated from the SSI. These data suggest that prophylactic antibiotics should be chosen from among those to which bacteria from the IABC are highly sensitive, and that therapeutic antibiotics should be chosen from among those to which bacteria isolated from the SSI are highly sensitive. In conclusion, the exploration of IABC enables prediction of the incidence of SSI.

The incidence of postoperative infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in Japan has been increasing dramatically¹³. In March 1990 special infection control doctors (ICDs) were assigned and comprehensive controls against MRSA infection were defined. A total of 3536 patients having digestive tract operations in one department were studied between September 1987 and August 1997. The authors changed the use of antibiotics to prevent postoperative infection. Cephalosporins were employed for surgery of the upper digestive tract, including oesophagus, stomach, duodenum and gallbladder. Cefotiam was employed for surgery of the lower digestive tract, liver and pancreas. In oesophageal resection the tracheal tube was extracted during the early postoperative period, and for cervical oesophagogastric anastomosis the autostitch was changed to layer-to-layer anastomosis. The authors achieved successful control of postoperative MRSA infection: the incidence decreased to 0.3 per cent (nine of 2703). In conclusion, their methods of control against postoperative MRSA infection imply that comprehensive measures of prevention, including the reviewed specification and usage of antibiotics and operative management, have been well implemented. The rate reported is the lowest of any domestic hospital or institute in Japan, suggesting a continued and significant decrease.

The release of cytokine by Kupffer cells during hypoxia-reoxygenation was studied *in vitro* in male Wistar rats with obstructive jaundice to investigate the kinetics of interleukin (IL) 8 release by Kupffer cells during hypoxia-reoxygenation and to study the influence of endotoxin during the reoxygenation period¹⁴. The rats were divided into two groups: one that underwent bile duct ligation and one that had a sham operation. Kupffer cells were isolated by collagenase digestion and centrifugal elutriation. The cells were first subjected to hypoxia (95 per cent nitrogen), after which they were reoxygenated (95 per cent oxygen). In addition, they were stimulated with lipopolysaccharide (LPS) 0, 1 and 10 ng/ml. In both groups the levels of IL-8 increased during the period of hypoxia-reoxygenation, and reoxygenation after hypoxia further intensified IL-8 production. During the period of hypoxia, IL-8 levels in the ligated group increased significantly compared with those in the sham group. With the LPS challenge there was no significant difference in IL-8 levels in either group. In conclusion, obstructive jaundice induces the activation of Kupffer cells, resulting in increased IL-8 production during hypoxia-reoxygenation.

A study was performed to investigate the effect of lymphatic blockage on the amount of endotoxin in portal venous blood, nitric oxide synthesis, the release of aspartate aminotransferase (ASAT) from the liver, hepatic damage and survival in an experimental model of dogs with peritonitis¹⁵. The dogs were divided into a control group (group 1), a group with unligated thoracic duct peritonitis (group 2) and a group with ligated thoracic duct peritonitis (group 3). Peritoneal fluid and blood from the portal vein and femoral artery were taken for peritoneal culture, endotoxin and ASAT assay respectively; liver biopsies were performed to assess hepatic damage and for nitric oxide assay. There was a higher bacterial count in the peritoneal fluid of animals in group 3 than in that from group 2 animals ($P < 0.0001$). Bacteria grew in all the blood cultures from the group 2 animals, but growth was seen only in blood cultures from four of the group 3 animals. The levels of endotoxin, nitrite and ASAT in group 3 were significantly increased in comparison with those in group 2 ($P < 0.0001$). Extensive hepatocellular necrosis with haemorrhage was observed in the livers of group 3 animals, all of whom died within 48 h. The results of this study suggest that the blockage of lymph flow has a negative effect on the liver and survival in dogs with peritonitis, and that hepatic damage is related directly to the amount of endotoxin to which the liver is exposed.

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Effect of liver blood flow and function on hepatic indocyanine green clearance measured directly in a cirrhotic animal model

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Background: Peripheral blood clearance of indocyanine green (ICG) has been used as a test of liver function but gives little information on biliary excretion. Hepatic ICG uptake and clearance can be measured directly by near-infrared spectroscopy (NIRS). Direct ICG measurement has not previously been correlated with liver blood flow and function in cirrhosis.

Methods: Two groups of New Zealand white rabbits ($n = 12$) underwent laparotomy for liver exposure. Cirrhosis was induced by feeding animals ($n = 6$) with a high-cholesterol (2 per cent) diet for 16 weeks. Hepatic blood flow and microcirculation were measured. Hepatic ICG concentration was measured directly using NIRS probes on the liver surface. From the ICG concentration–time curve, hepatic ICG uptake and excretion rates were calculated by a non-linear least square curve fitting method.

Results: There was a significant reduction in ICG uptake rate (mean(s.d.) $0.300(0.130)$ versus $2.040(0.420) \text{ min}^{-1}$; $P = 0.0001$) and ICG excretion rate ($0.007(0.009)$ versus $0.227(0.096) \text{ min}^{-1}$; $P = 0.002$) in cirrhotic animals. The hepatic ICG uptake rate correlated with hepatic blood flow and flow in the microcirculation ($r = 0.81$, $P = 0.002$; $r = 0.92$, $P < 0.001$, respectively). The hepatic ICG excretion rate was significantly associated with indicators of impaired liver function including bilirubin ($r = -0.86$, $P = 0.0004$), aspartate aminotransferase ($r = -0.81$, $P = 0.001$) and lactate dehydrogenase ($r = -0.83$, $P = 0.0008$).

Conclusion: ICG uptake measured directly by NIRS reflects the reduced liver blood flow and perfusion in cirrhosis and its excretion correlates with the degree of liver parenchymal dysfunction. This technique may allow a more accurate method of liver function assessment than peripheral blood ICG clearance.

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Introduction

Surgical intervention in patients with abnormal liver function carries a higher morbidity and mortality rate than in those with normal liver function¹. It is therefore crucial to assess liver function before operation to identify hepatic functional reserve and predict surgical risk. Quantitative liver function assessment can provide information on the likely outcome of surgery^{2,3}. Biochemical tests currently in use lack both sensitivity and specificity^{4,5}. There are no non-invasive methods available for assessment of individual lobar function.

Indocyanine green (ICG) is a synthetic dye that has been used for many years to measure hepatic blood flow^{6–8} and as a test of liver function by measuring its blood clearance after

intravenous administration. It has been used to evaluate donor liver function before⁹ and after¹⁰ liver transplantation. It has also been widely investigated in determining the prognosis of patients with cirrhosis¹¹. Conventionally ICG handling by the liver is predicted from its blood clearance curve⁷. Ott *et al.*¹², however, have suggested that the ICG plasma clearance curve contains no information about liver–bile interaction.

Hepatic blood flow is assessed by measuring the maximum extraction of ICG from blood while keeping the plasma ICG level constant. Clinical application of this method is difficult and unreliable¹³. In addition liver–bile interaction and excretion of ICG is not reflected by peripheral blood ICG measurement¹⁴.

Direct measurement of hepatic ICG concentration could provide an accurate way to study ICG kinetics in the liver,

including uptake and excretion. ICG can be quantified using near-infrared spectroscopy (NIRS) because of its characteristic maximum absorption peak at 805 nm in the near-infrared light region. NIRS is a light-based non-invasive technique originally developed for monitoring tissue oxygenation in neonatal brain¹⁵. In an animal model of acute hepatic dysfunction, hepatic ICG uptake and excretion rates measured by NIRS accurately reflected liver perfusion and function, respectively¹⁶.

The aim of the current study was to determine the relationship between hepatic circulation and function in a cirrhotic animal model, and ICG uptake and excretion rates measured directly from the liver parenchyma by NIRS.

Materials and methods

Experimental groups and induction of cirrhosis

The study was conducted under a licence granted by the Home Office in accordance with the Animals (Scientific Procedures) Act 1986. New Zealand white rabbits ($n = 12$; mean(s.d.) weight 3.9(0.4) kg) were used in this experiment: six controls and six with cirrhosis. Cirrhosis was induced by feeding animals with a high-cholesterol (2 per cent) diet, 150 g/day for 16 weeks. Liver function was determined by measuring bilirubin, aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) levels using a standard clinical automated analyser from a venous blood sample (250 µl) taken at the time of the experiment.

Anaesthesia and surgical procedure

Anaesthesia was induced using Hypnorm 0.5 ml/kg (fentanyl-fluanisone; Janssen-Cilag, High Wycombe, UK) and diazepam 2.5 mg/kg given intramuscularly, and maintained with halothane via a standard anaesthetic circuit. Body temperature was maintained by a warming blanket at 37–38.5°C (Homeothermic blanket control unit; Harvard Apparatus, Southmattick, Massachusetts, USA). A pulse oximeter (Ohmeda Biox 3740 pulse oximeter; Ohmeda, Louisville, Colorado, USA) was used for continuous monitoring of arterial oxygen saturation and heart rate. Catheters were inserted into the right femoral artery and vein for arterial blood pressure monitoring and fluid administration respectively. Normal saline solution was given during the experiment at a rate of 10 ml per kg per h to compensate for intraoperative fluid loss.

Laparotomy was performed through a midline incision. The ligamentous attachments from the liver to the diaphragm were divided and the liver was exposed. The hepatic artery and portal vein were exposed. For continuous

measurement of total hepatic blood flow, a transonic ultrasonic flowmeter system (HT207; Transonic Medical System, Ithaca, New York, USA) was used with perivascular flow probes 1 mm in diameter for hepatic artery blood flow and 4 mm for portal vein blood flow. Hepatic microcirculation was measured by a surface laser Doppler flowmeter (LDF) (DRT4; Moor Instruments, Axminster, UK) in flux units. Portal venous pressure was measured with a pressure transducer connected to a central data analysis computer (MacLab; Apple Computers, Cupertino, California, USA) by cannulating a branch of the portal vein.

ICG was prepared just before injection and dissolved in sterile water at a concentration of 1 mg/ml. After acquisition of a baseline reading, a bolus of ICG 0.5 mg/kg (Cardiogreen, 90 per cent dye content; Sigma Chemical Company, Poole, UK) was given via the femoral vein in 20 s.

Liver biopsies (2 × 5 mm) were taken from the right lobe of the liver at the start of the experiment. The biopsies were fixed in neutral buffered formalin (10 per cent) and embedded in paraffin; blocks were cut into sections 5 µm thick for haematoxylin and eosin, and reticulin staining. Histological examination of the liver biopsies was conducted by an experienced pathologist.

Near-infrared spectroscopy

NIRS depends upon the relative transparency of biological tissue to light in the near-infrared region (700–1000 nm). Light at visible wavelengths (400–700 nm) is strongly attenuated in tissue and as a result can only penetrate a maximum distance of approximately 10 mm^{17,18}. However, light is absorbed less by tissue at near-infrared wavelengths, and with sensitive detectors it is then possible to detect light that has traversed up to 80 mm of tissue^{18–20}.

NIRS depends upon the light absorption properties of key biochemical components and can be used to measure concentration changes of haemoglobin as well as ICG. The concentration change in these chromophores can be quantified using a modified Beer–Lambert Law. The NIRS instrument (NIRO-500; Hamamatsu Photonics, Hamamatsu, Japan) used in this study produces light at four wavelengths which is transmitted in sequential pulses via a bundle of optical fibres (probes) to the liver. Photons emerging from the liver are collected by the second bundle of optical fibres and detected by a photomultiplier tube. The difference between transmitted and received light intensity at each wavelength was used to determine the optical density changes at each wavelength. A modified computer program was used to compute continuously the changes in hepatic ICG concentration based on its absorption coefficient, which has been validated in a previous study¹⁶.

Analysis of hepatic indocyanine green concentration curve with near-infrared spectroscopy

For continuous monitoring of hepatic ICG concentration NIRS probes were positioned, with a 20-mm separation, on the liver surface with a 4-Hz sampling time. This produces a concentration–time curve. This curve was analysed to produce two exponential rate constants, representing hepatic ICG uptake rate (α) and hepatic ICG excretion rate (β). These rate constants were calculated by fitting the ICG concentration–time curve to a two-compartment mathematical model as defined by the sum of two exponential equations²¹:

$$\text{ICG}(t) = -A \times \exp(-\alpha \times t) + B \times \exp(-\beta \times t)$$

where ICG(t) is the hepatic concentration of ICG at any time (t), and α and β (per minute) are the rate constants for hepatic ICG uptake and excretion respectively. A and B are the zero time intercepts, both theoretically equal to the initial hepatic concentration. The assumption is that α is greater than β and that A is approximately equal to B .

The fitting to this model was done using a commercial computer package based on the non-linear least square regression (GraphPad Prism; GraphPad Software, San Diego, California, USA). The iterative procedure of the program minimizes the reduced sum of squares. The goodness of the fit was evaluated by the R^2 value.

Intrahepatic portal vascular resistance

From the pressure and flow data, the intrahepatic portal vascular resistance (IHPR) was calculated according to the following formula:

$$\text{IHPR} = P/Q$$

where P is the portal venous pressure (millimetres of mercury) and Q the portal venous flow (millilitres per minute).

Statistical analysis

Values are expressed as mean(s.d.). For comparison between the two experimental groups Student's t test was used. $P < 0.05$ was considered statistically significant. The relationship between hepatic ICG uptake rate and hepatic microcirculation was tested using the Pearson correlation coefficient.

Results

Induction of cirrhosis

With a high-cholesterol diet, all animals became cirrhotic over a 16-week period as demonstrated by clinical ascites, the macroscopic appearance of the liver and the portal pressure at laparotomy, and confirmed by liver histology. At laparotomy, ascites ranging from 10 to 20 ml was found in cirrhotic animals and varices at the low gastric border. The liver appeared pale and nodular.

Blood flow and parenchymal perfusion in cirrhosis

There was a significant reduction in portal venous, hepatic arterial and total hepatic blood flow by 30(9), 31(4) and 30(10) per cent respectively in cirrhotic animals compared with normal controls (*Table 1*). In cirrhotic animals, the portal venous pressure was significantly increased (*Table 1*). IHPR calculated from pressure and flow data was significantly increased in cirrhotic animals (0.194(0.030) *versus* 0.042(0.025) mmHg.min per ml in normal controls; $P < 0.001$). The hepatic microcirculation, measured with LDF, was significantly reduced in cirrhotic animals compared with controls (79(14) *versus* 228(19) flux units; $P < 0.001$) (*Table 1*).

Table 1 Hepatic haemodynamic data in cirrhotic and normal rabbits

	Control ($n=6$)	Cirrhotic ($n=6$)	P^*
PVBF (ml/min)	96(8)	67(13)	<0.001
HABF (ml/min)	13(4)	9(3)	<0.001
THBF (ml/min)	109(6)	76(10)	<0.001
Portal vein pressure (mmHg)	4(2)	13(4)	<0.001
Hepatic microcirculation (flux)	228(19)	79(14)	<0.001
IHPR (mmHg.min per ml)	0.042(0.025)	0.194(0.030)	<0.001
MABP (mmHg)	85(6)	89(7)	0.32
Heart rate (beats/min)	210(15)	206(20)	0.71

Values are mean(s.d.) of six animals in each group. PVBF, portal vein blood flow; HABF, hepatic artery blood flow; THBF, total hepatic blood flow; IHPR, intrahepatic portal vascular resistance; MABP, mean arterial blood pressure. *Student's t test

Liver function and histology of cirrhotic animals

At baseline, liver function in cirrhotic animals was grossly abnormal with raised levels of bilirubin, AST and LDH (Table 2). Histological examination of liver biopsies from cirrhotic animals revealed extensive damage of plates of hepatocytes, hepatic necrosis, fibrosis and portal bridging (Fig. 1).

Hepatic indocyanine green clearance measured with near-infrared spectroscopy

There was a significant reduction in ICG uptake rate ($0.300(0.130)$ versus $2.040(0.420)$ min⁻¹; $P=0.0001$) and hepatic ICG excretion rate ($0.007(0.009)$ versus $0.227(0.096)$ min⁻¹; $P=0.002$) in cirrhotic animals compared with the normal controls (Table 2). Fig. 2 shows typical examples of hepatic ICG concentration–time data and their fitting curves in control and cirrhotic groups. Hepatic ICG rate of uptake was strongly associated with total hepatic blood flow ($r=0.81$, $P=0.002$; Fig. 3) and flow in the hepatic

Table 2 Liver function and hepatic indocyanine uptake and excretion rates in control and cirrhotic rabbits

	Control	Cirrhotic
Bilirubin (μ mol/l)	2.8(1.2)	77.3(11.3)*
AST (units/l)	33.5(5.2)	153.0(37.9)*
LDH (units/l)	18.7(2.8)	2069.0(414.9)*
α (min ⁻¹)	2.040(0.420)	0.300(0.130)*
β (min ⁻¹)	0.227(0.096)	0.007(0.009)†

Values are mean(s.d.) of six animals in each group. AST, aspartate aminotransferase; LDH, lactate dehydrogenase; α , hepatic indocyanine green (ICG) uptake rate; β , hepatic ICG excretion rate; * $P<0.001$, † $P<0.05$ versus control (Student's *t* test)

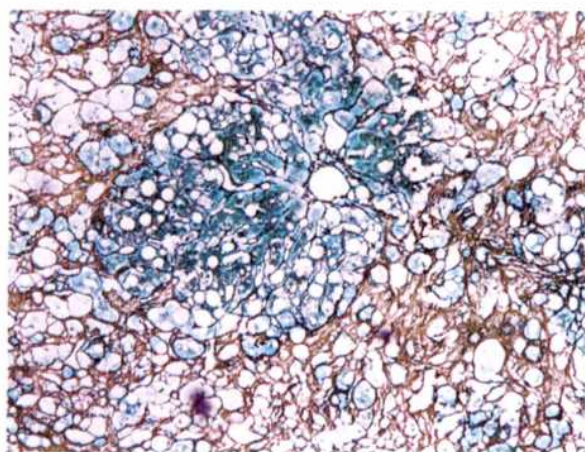


Fig. 1 Histological features of cirrhotic rabbits showing extensive fibrosis and destruction of plates of hepatocytes (reticulin stain, original magnification $\times 400$)

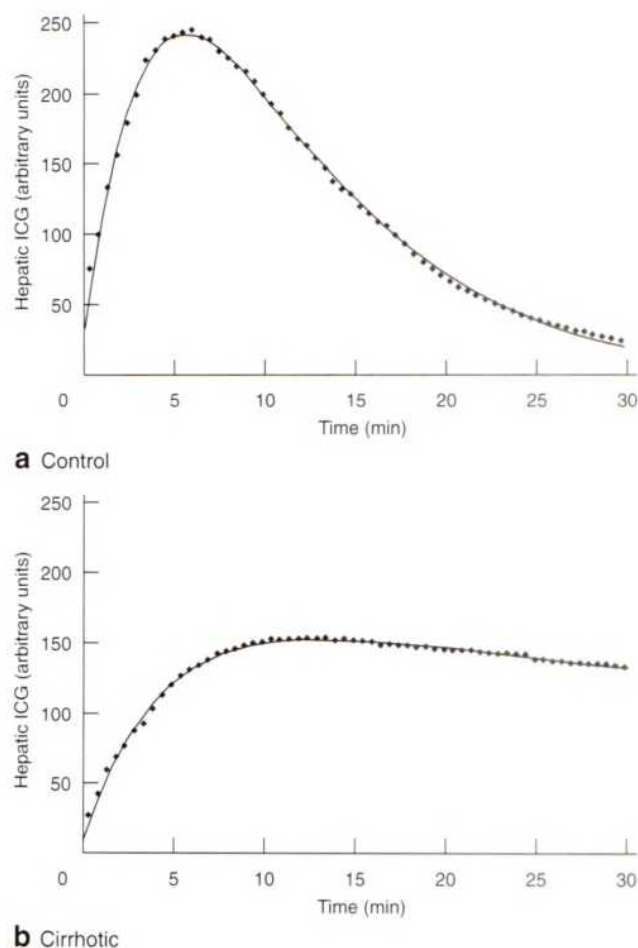


Fig. 2 Typical fitting curve of indocyanine green (ICG) clearance in **a** control and **b** cirrhotic rabbits ($R^2=0.99$ for each plot)

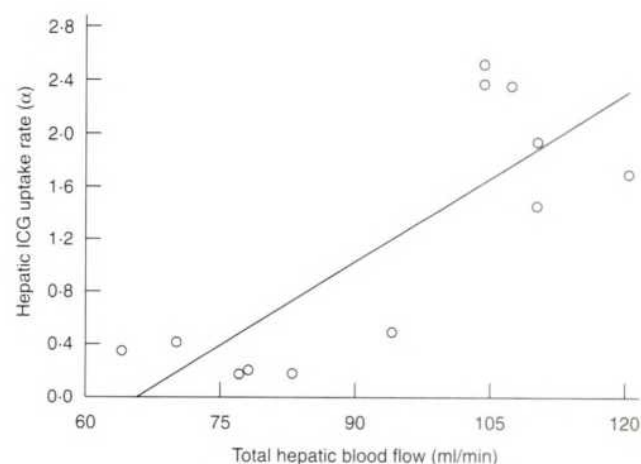


Fig. 3 Correlation between indocyanine green (ICG) uptake and total hepatic blood flow. $n=12$, $r=0.81$, $P=0.002$

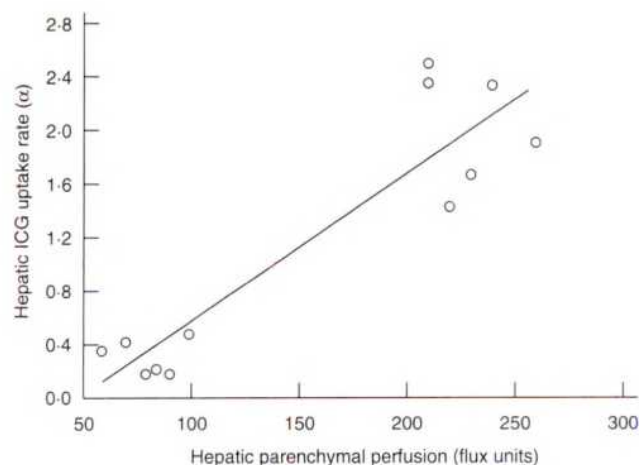


Fig. 4 Correlation between indocyanine green (ICG) uptake and total hepatic blood flow. $n = 12$, $r = 0.92$, $P < 0.001$

microcirculation ($r = 0.92$, $P < 0.001$; Fig. 4). A significant negative correlation was present between the hepatic ICG excretion rate and levels of bilirubin ($r = -0.86$, $P = 0.0004$), AST ($r = -0.81$, $P = 0.001$) and LDH ($r = -0.83$, $P = 0.0008$).

Discussion

The current study was designed to correlate the changes in hepatic blood flow, microcirculation and function in cirrhosis with a direct measure of hepatic ICG using NIRS. The calculated rates of ICG uptake correlated well with liver perfusion and ICG excretion with biochemical markers of liver dysfunction.

Rabbits given a high cholesterol diet together with diethylstilboestrol have been shown to develop hepatic fibrosis^{22,23}. The method was simplified by feeding the rabbits with a cholesterol-rich diet alone²⁴. During induction of cirrhosis over 16 weeks there were no deaths with this diet. The cirrhotic animals showed characteristic features of extensive fibrosis and bridging on liver biopsies. Clinically, there was evidence of ascites, varices and grossly abnormal liver function. Haemodynamically, there was an increase in the portal venous pressure and IHP, a reduction in portal venous and hepatic arterial flow and an impaired hepatic microcirculation. In this model of liver cirrhosis, features of portal hypertension and liver cirrhosis were similar to those seen in humans in terms of haemodynamics and liver function²⁴. However, despite a long period of dietary modification to induce liver damage, regenerative cirrhotic nodules were not found.

In this study ICG uptake and clearance related to hepatic blood flow and function in a cirrhotic animal model were assessed. Although ICG is highly bound to albumin and α -lipoproteins^{25,26}, its elimination is solely by the liver with

no extrahepatic metabolism or excretion^{25,26}. It is excreted in the bile without metabolic alteration or conjugation via transport by glutathione S-transferase and it does not undergo enterohepatic circulation^{25,26}. The hepatobiliary transport of ICG is affected by various factors such as hepatic blood flow; binding to plasma proteins; influx across the sinusoidal plasma membrane; intracellular transport and interaction with cytoplasmic binding proteins and organelles; transport across the biliary canalicular membrane; and bile flow^{27,28}. Its excretion across the canalicular plasma membrane is adenosine 5'-triphosphate (ATP) dependent²⁹⁻³¹. The reduction of ICG uptake in cirrhotic animals could be secondary to the observed reduction in hepatic blood flow and microcirculation owing to the occurrence of capillarization and collagenization, increased intrahepatic vascular resistance and an impaired hepatic microcirculation^{32,33}. In addition, the sinusoidal space was reduced in this model because of mechanical compression of the adjacent vasculature by fat in the hepatocytes which has been shown to reduce total hepatic blood flow and flow in the hepatic microcirculation³⁴. LDF confirmed a diminished hepatic microcirculation in cirrhotic livers compared with controls. A significant positive correlation between hepatic ICG uptake rate and both hepatic blood flow and microcirculation indicates that direct measurement of ICG uptake by NIRS could be used as an index of hepatic blood flow in cirrhosis.

ICG elimination across the canalicular membrane involves cytoplasmic transport and biliary excretion, which are ATP dependent²⁹⁻³¹. In cirrhosis, there is an abnormality in hepatocellular function from destruction of hepatocytes and an increase in sinusoidal capillarization and collagenization^{32,33} which reduces sinusoidal diffusion, intracellular tissue oxygenation and ATP production. Reduced ATP production is well recognized with fatty change and cirrhosis of the liver³⁵ and may directly influence ICG excretion. Impairment of liver function in cirrhosis was strongly correlated with a reduction in ICG clearance.

The evaluation of ICG uptake and clearance directly from the liver using NIRS clearly correlates well with liver perfusion and function in this cirrhotic animal model. This direct measurement of ICG from the liver may avoid the inaccuracies inherent in assessing liver function from the measurement of peripheral blood clearance of ICG¹². Having established the methodology for ICG assessment by NIRS, the clinical applications require to be addressed. A potential role would be in circumstances in which information on liver perfusion and function are essential, such as liver surgery or transplantation. Currently the technique requires use of probes on the liver surface and can therefore only be used as an operative tool. However, current

developments may allow insertion of probes at laparoscopy and placing of indwelling probes for monitoring. Such techniques could be applied to patients with chronic liver disease who require functional assessment before surgery. However, the information obtained on liver function by ICG clearance is additional to that obtained by NIRS on oxygen supply and metabolism, including changes in liver parenchymal haemoglobin oxygen saturation and cytochrome oxidase activity that correspond directly to ATP formation. The potential of this technique is therefore to provide a complete profile of liver function and bioenergetics from which to optimize the recovery and drug treatment of patients undergoing liver surgery or transplantation.

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Preoperative staging of rectal cancer allows selection of patients for preoperative radiotherapy

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Background: Variability in rates of local recurrence following resection of rectal cancer has led to the suggestion that all patients should undergo preoperative radiotherapy. This centre employs a selective policy of radiotherapy only in patients with evidence of advanced local disease determined by preoperative staging.

Methods: A retrospective review was carried out of 114 consecutive patients with rectal cancer. Patients were divided before operation into palliative and curative groups based on preoperative staging. Only patients in the palliative group were offered preoperative radiotherapy. Total mesorectal excision (TME) was performed for all tumours of the middle or lower rectum.

Results: The perioperative mortality rate was 0.9 per cent and anastomotic dehiscence occurred in 2.8 per cent. Local recurrence developed in 4 per cent of patients in the 'curative' group and in seven of 15 of those assigned to the palliative group before operation ($P < 0.01$). Positive lateral resection margins were significantly associated with a risk of subsequent recurrence (ten of 13 *versus* three (3 per cent) of 93; $P < 0.001$).

Conclusion: Preoperative adjuvant radiotherapy can be omitted reasonably in patients in whom there is no evidence of locally advanced disease, provided that adequate surgery, incorporating TME for low tumours, is performed.

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Introduction

The reported local tumour recurrence rate after surgery for rectal cancer varies from 2.6 to 50 per cent^{1–5}. Factors that have been shown to influence local recurrence include tumour morphology⁶, stage of disease⁷, evidence of local extension⁸, tumour fixity⁹ and the surgical technique employed at the operation¹⁰.

In response to the observation that tumour deposits occur in the mesorectum of up to 20 per cent of pathological specimens of resected rectal cancer, total mesorectal excision (TME) *en bloc* with the rectum has been advocated^{11,12}. Local recurrence rates of less than 5 per cent after 'curative resection' have now been attributed to TME in several studies^{3,4,13}. These reports, however, have been criticized for two reasons. First, the definition of 'curative' was made by the surgeon at operation, and the benefits gained could therefore be due to 'stage drift' rather than surgical technique. Second, the technique of TME produces a devascularized stump of rectum and consequently

has been associated with high rates of anastomotic dehiscence³, a complication which, paradoxically, is associated with a high local recurrence rate.

Given the excellent results of surgery using TME, the role of preoperative radiotherapy is now uncertain. Several studies have shown a reduction in local recurrence with a survival benefit for patients receiving preoperative radiotherapy compared with those receiving surgery alone^{14–16}. Unfortunately the local recurrence rate in the treatment groups (surgery plus radiotherapy) in these studies was higher than that reported in studies of TME alone^{3,4,13}. It is important that this discrepancy is clarified since preoperative radiotherapy has been advocated in guidelines for the management of colorectal cancer¹⁷ and is the subject of the MRC CRO7 clinical trial.

An attempt has been made to clarify this difficult area in two ways. First, by using preoperative staging, patients have been allocated objectively to curative and palliative groups before surgery. Second, an anastomosis above a long devascularized rectal stump has been avoided, but the goals

of TME have been achieved by performing a proctectomy and double-stapled coloanal anastomosis for tumours less than 10 cm from the anal verge. TME has not been used for upper rectal cancers in this series. The results of the present study incorporating preoperative staging and a modified surgical technique are presented.

Patients and methods

One hundred and fourteen consecutive patients with rectal cancer (lower margin at 16 cm or less), who presented to a single surgeon between August 1986 and December 1995, were studied. Eight of these 114 patients did not undergo surgical resection of the primary tumour; one patient refused surgery while the remaining seven were considered unfit for resection and had advanced metastatic disease. These patients were offered palliative care.

One hundred and six patients underwent resection of the primary tumour. Before operation all patients had the presence of the primary tumour confirmed by histological examination and had examination under anaesthesia and/or pelvic computed tomography (CT), depending on whether the tumour was easily palpable. On the basis of these investigations, patients with evidence of tumour extension to adjacent organs, loss of clear margins around the tumour or fixity at examination under anaesthesia were allocated to the 'palliative' group and offered preoperative radiotherapy (45–50 Gy over 5–6 weeks). Patients who had evidence of hepatic metastases on CT were also allocated to the palliative group but were not given radiotherapy. The remaining patients with no evidence of locally advanced disease on CT or EUA were allocated to the 'curative' group.

Operative technique

In all 106 patients a laparotomy was performed. Any patient found to have unexpected hepatic metastases was allocated to the palliative group. All patients allocated before operation to the curative group underwent resection of the primary tumour. The rectum and mesorectum were mobilized *en bloc* under direct vision using a diathermy dissection technique. In patients in whom the lower margin of the tumour lay at approximately 10 cm or less from the anal verge, the rectum was transected at the level of the upper anal canal using a stapling instrument (RL30; Ethicon, Edinburgh, UK). Intestinal continuity was restored by the double-stapled technique (DCH 29; Ethicon). A defunctioning loop ileostomy was used after all double-stapled coloanal anastomoses. In patients in whom the lower edge of the tumour was between 10 and 16 cm from the anal verge, a 5-cm clearance margin was obtained below

the tumour and the mesorectum was divided obliquely at that level. Intestinal continuity was then achieved by a single-layer interrupted handsewn anastomosis without a covering ileostomy. An abdominoperineal resection was performed if a 2-cm clearance margin could not be achieved without compromising the anal sphincters.

All patients were reviewed at a follow-up clinic 6 weeks after surgery and at 3-month intervals for the first 2 years, every 6 months for a further 2 years and annually thereafter. Investigations were performed when clinically indicated during follow-up. At 2 years, however, each patient underwent rigid proctoscopy and ultrasonography of the liver. At 5 years a colonoscopy was performed.

Statistical analysis

Statistical analysis was by means of Fisher's exact test and significance was assumed at $P < 0.05$.

Results

One hundred and six patients with a median age of 68 (range 41–86) years underwent resection of the primary rectal cancer. The male : female ratio was 2 : 1. Follow-up was for a minimum period of 24 (median 58, range 24–132) months. Preoperative staging was performed in 98 of the 106 patients (EUA in 58 patients and CT in 40). The remaining eight patients were not staged before operation because of the urgency of surgery or for administrative reasons. These patients were allocated to the curative group for the purposes of the study.

The Dukes stage in the patients studied was subsequently shown to be A (11 per cent), B (48 per cent) and C (41 per cent). One of the 106 patients who underwent resection died 28 days after surgery from a cerebrovascular accident (operative mortality rate 0.9 per cent). A further three patients (2.8 per cent) developed clinical evidence of anastomotic dehiscence.

On the basis of preoperative staging, 76 patients were allocated to the curative group. At operation, 26 (34 per cent) of these 76 patients had tumours at or above 10 cm which were resected by traditional handsewn anterior resection without complete excision of the mesorectum; 32 patients (39 per cent) had low rectal tumours and had a double-stapled coloanal anastomosis with TME. Twelve patients (17 per cent) underwent abdominoperineal resection, again with TME. Six patients (10 per cent) underwent a Hartmann's procedure, three of whom presented as an emergency. Of these 76 patients in the curative group, three (4 per cent) subsequently developed local recurrence during follow-up (Fig. 1); a further ten patients (13 per cent) have

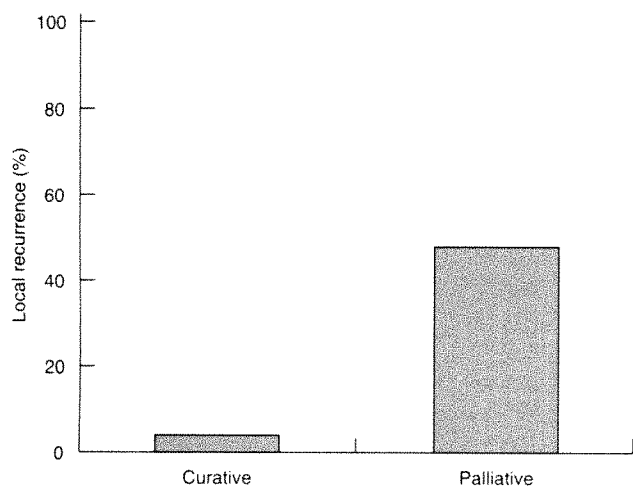


Fig. 1 Local recurrence in patients placed into 'palliative' and 'curative' groups before operation

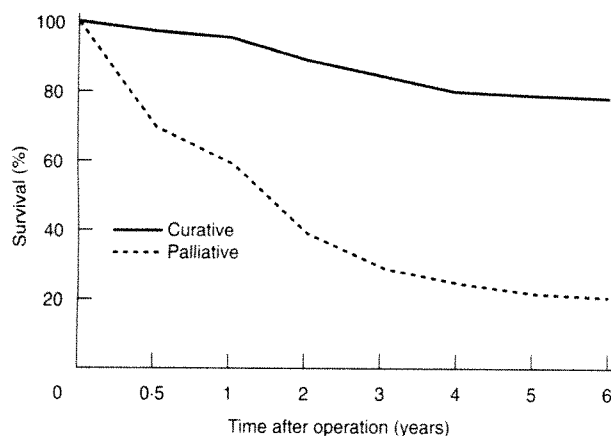


Fig. 2 Survival of patients placed into 'palliative' and 'curative' groups before operation

developed evidence of disseminated disease. The remaining 63 patients remain alive and well and apparently disease free.

Thirty patients were allocated to the palliative group. Of these, 15 had evidence of liver metastases, all of whom have died or have evidence of progressive hepatic disease. The remaining 15 patients were allocated to the palliative group on the basis of locally advanced disease demonstrated on CT or EUA; these patients were all offered radiotherapy before operation. Ten of these 15 patients have subsequently died from advanced systemic (three) or local (seven) disease. The remaining five patients in the palliative group remain alive and well with no evidence of disease. These five patients all had lateral resection margins that were free of tumour.

On histological examination, positive lateral resection margins were found in one patient in the curative group and in 12 in the palliative group. Local recurrence subsequently occurred in ten of 13 patients with a positive resection margin compared with three (3 per cent) of 93 patients who had a negative resection margin ($P < 0.001$).

Overall, 63 (83 per cent) of the 76 patients in the curative group remain alive and well compared with five of the 30 patients in the palliative group ($P < 0.01$) (Fig. 2).

Discussion

Local recurrence after an apparently curative resection for rectal carcinoma is an important event since it is often fatal. Even in the absence of disseminated disease, less than 5 per cent survive 5 years in the absence of surgical intervention¹⁸. Given that local recurrence has been shown at autopsy to be limited to the pelvis in 25–50 per cent of patients^{19,20}, any measure that would reliably prevent local recurrence would also have a major impact on survival for rectal cancer. It is important to note, therefore, that it has recently been suggested that two measures (the surgical technique of TME and the use of preoperative radiotherapy) substantially reduce local recurrence^{3,4,14,16}. Although aggressive multimodality regimens of preoperative chemoradiation have been described with some success, the morbidity and treatment-related mortality rates remain high²¹.

TME has been associated with local recurrence rates after 'curative surgery' of less than 5 per cent in several studies^{3,4,13}. The technique is based on the pathological observation that rectal cancer may spread into the mesorectum and that wide clearance of the lateral resection margins is necessary²². TME, however, as originally described, leaves a long cuff of rectum which is potentially devascularized, giving rise to high anastomotic leakage rates (16.5 per cent in Heald's initial series³). Further, the definition of 'curative' in those studies was determined by the surgeon at operation, leading to the possibility that there may have been 'stage drift' (good-risk patients in the curative group and doubtful patients in the palliative group). There is some support for the view that this may have occurred inadvertently in that only 20 per cent of patients in the palliative group in one study subsequently developed local recurrence³.

The principal aim of the present study was to overcome this problem by allocating patients objectively to the curative and palliative groups before surgery on the basis of preoperative staging. The results confirm that very low local recurrence rates can be achieved after curative surgery defined on this basis; in the present study 4 per cent. This compares with studies in which the surgeon selected the 'cures' where the local recurrence rates were also less than 5

per cent. It is of interest to note that all but one patient in whom CT was reported as not involving adjacent structures had clear lateral and distal resection margins on subsequent pathological examination. This is important when considering the role of preoperative radiotherapy.

With the development of effective preoperative adjuvant therapy regimens, preoperative staging has received greater attention²³. The accuracy of digital examination increases with operator experience and tumour fixation to adjacent structures can be recognized in up to 83 per cent of cases. Transrectal ultrasonography is a helpful staging technique, particularly with the increasing use of local excision for early rectal tumours. This appears, however, to be stage dependent; while reliable results can be obtained for T₁ and perhaps T₂ lesions, tumours that extend through the rectal wall are less accurately staged. CT and magnetic resonance imaging (MRI), in contrast, are less accurate at imaging the individual layers of the bowel wall. Extension into adjacent organs is effectively shown, however, with obliteration of the tissue planes between the viscera. CT or MRI would therefore appear to be more accurate when staging advanced tumours and may therefore be more useful in determining which patients would benefit from preoperative adjuvant therapy.

The palliative group in the present study comprised 15 patients who had advanced metastatic disease and a further 15 patients who were considered, on the basis of preoperative staging, to have locally fixed primary tumours. Of the latter 15 patients, only ten died from advancing disease. The remaining five patients remain well with no evidence of tumour recurrence. Although the follow-up may be considered short in some patients, it was a minimum of 2 years, during which time the majority of clinical recurrences would have occurred²⁴. The five surviving patients may have been overstaged by CT owing to a peritumour inflammatory reaction. An alternative explanation is that the tumours were downstaged by preoperative radiotherapy. Crucially the five surviving patients had tumour-free lateral resection margins at final pathological examination. The palliative group as a whole, however, had a very poor outcome with only five surviving disease free. This raises the question of whether these patients would derive benefit from a more aggressive form of multimodality preoperative treatment, such as combination chemoradiotherapy.

TME was used for low rectal tumours as part of a proctectomy and double-stapled anastomotic technique. This allows TME with a low anastomotic leak rate, in the present study 2.8 per cent. To assess the impact of the specialist surgical technique of TME, it is necessary to consider the mortality and local recurrence rates for the entire study. In total, 13 patients (12 per cent) in the present

study developed local recurrence which is low compared with historical series in which local recurrence rates of 40 per cent and higher have been reported^{1,2,25}. Although the patients in the present study were treated by a single specialist surgeon, they were not otherwise selected, and included elective and emergency patients, predominantly drawn from the catchment area of the hospital. Further evidence of non-selection was found in the pattern of Dukes staging which is comparable to that in reports of the Scottish population as a whole. These factors may support the suggestion, therefore, that there was a true reduction in local recurrence attributable to the surgical technique. Only a randomized trial of TME *versus* no TME would answer this question unequivocally.

The results of the present study also go some way towards clarifying the role of radiotherapy in rectal cancer. Although postoperative radiotherapy has, in some studies, led to a decrease in rates of local recurrence, it has not been associated with increased survival^{24,25}. Preoperative radiotherapy has, in contrast, been shown to improve both local recurrence rates and enhance survival^{16,17}. However, without the benefit of full pathological assessment of the resection margins, patients have not, to date, been stratified into high- and low-risk subgroups. All patients must therefore receive preoperative adjuvant treatment in order that the minority may benefit. In addition to the cost implications, radiotherapy has been shown to be associated with significant adverse effects. It is therefore desirable to target radiotherapy to patients at high risk of local recurrence, avoiding unnecessary radiotherapy to low-risk groups. In the present study radiotherapy was avoided in 91 patients, of whom, in retrospect, only three may have benefited.

In conclusion, preoperative staging allows the selection of a subgroup of patients at high risk of local recurrence and thus adjuvant preoperative radiotherapy may be offered only to this subgroup of patients (14 per cent) without compromising cure in the remaining patients. TME was incorporated in the surgical technique, but only in patients who had tumours within 10 cm from the anal verge. These data suggest that patients can be classified into 'palliative' and 'curative' groups before operation, and that preoperative adjuvant therapy can reasonably be omitted in patients in whom there is no evidence of locally advanced disease, provided that adequate surgery, incorporating TME for low tumours, is performed.

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Reduced endothelin-3 expression in sporadic Hirschsprung disease

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Background: Enteric aganglionosis in Hirschsprung disease has been linked to genes coding for endothelin-3 (*EDN3*) and the endothelin B receptor (*EDNRB*), but there is no such linkage in most patients with sporadic Hirschsprung disease. However, the similarity between the distal colonic aganglionosis in Hirschsprung disease and that due to *EDN3* or *EDNRB* mutations led to the hypothesis that levels of expression of these genes might be affected in the absence of mutation, thus causing the Hirschsprung disease phenotype. The aim of this study was to determine *EDN3* and *EDNRB* messenger RNA (mRNA) levels in tissue samples from patients with sporadic Hirschsprung disease.

Methods: RNA and DNA were isolated from the ganglionic and aganglionic colonic segments of ten children with sporadic Hirschsprung disease, and from the colon of ten age-matched controls. The DNA was analysed for mutations in the genes coding for endothelin-3 (ET-3) and endothelin B receptor (ET-B) proteins. Relative levels of *EDN3* and *EDNRB* mRNA were determined by semi-quantitative transcriptase-polymerase chain reaction.

Results: Three children had sequence variants in *EDN3* and *EDNRB*. In the remaining seven patients, *EDN3* mRNA levels were reduced in both the ganglionic and aganglionic colon compared with levels in controls; there was no difference in expression of *EDNRB* between groups.

Conclusion: In the absence of mutation, *EDN3* is downregulated in short-segment Hirschsprung disease, suggesting that this may be a common step leading to aganglionosis.

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Introduction

Hirschsprung disease is the most common neurocristopathy, affecting one in 5000 newborns. There is a positive family history in 7 per cent of cases¹. Absence of ganglion cells in a variable segment of the gut results in neonatal gastrointestinal obstruction. About 20 per cent of cases of Hirschsprung disease are 'long segment', the aganglionosis extending proximal to the sigmoid colon¹. More commonly, however, aganglionosis is restricted to the sigmoid colon and rectum in the short-segment form of the disease.

Gene mapping studies in patients and targeted gene deletions in animals have implicated several genes in the pathogenesis of Hirschsprung disease, including the tyrosine kinase receptor Ret together with its ligand glial cell-derived neurotrophic factor (GDNF)^{2–6}, and the endothelin B receptor (ET-B) together with its ligand endothelin 3 (ET-3)^{7–9}. However, mutations in the genes coding for these proteins (*RET*, *GDNF*, *EDNRB* and *EDN3*

respectively) taken together account for only 20 per cent of sporadic cases and 50 per cent of familial cases of Hirschsprung disease¹⁰. With the fact that sporadic disease is far more common than familial disease, it is clear that mutations in these genes are not the cause of most cases of Hirschsprung disease.

In contrast to the extensive aganglionosis caused by inactivation of the Ret-GDNF system^{4,10}, targeted disruption of genes coding for ET-B or ET-3 in homozygous mice leads to distal colonic aganglionosis which resembles that of short-segment Hirschsprung disease in humans^{7,8}. The objective of this study was to test the hypothesis that the sporadic Hirschsprung disease phenotype, while not resulting from mutations in *EDN3* or *EDNRB* *per se*, may result from a deficit in *EDN3* or *EDNRB* expression. *EDN3* and *EDNRB* messenger RNA (mRNA) levels were measured in children with Hirschsprung disease who had been screened to exclude mutations in *EDN3*, *EDNRB*, *RET* and *GDNF*.

Patients and methods

Patient population

This study was approved by the local research ethics committee. Specimens of ganglionic and aganglionic colon were obtained from ten consecutive patients with Hirschsprung disease at the time of pull-through procedure (surgical excision of the aganglionic segment). All cases of Hirschsprung disease were sporadic; eight patients had short-segment disease, one long-segment disease, and one total colonic aganglionosis. No major syndromic associations were detected other than one child with Down syndrome. A further ten colonic specimens were obtained from age-matched patients without Hirschsprung disease who were undergoing routine colostomy closure with normal bowel function at the time of closure. With the exception of the non-short-segment Hirschsprung disease cases ($n=2$), all colonic specimens were obtained from the sigmoid colon. Samples from patients with Hirschsprung disease were also sent for routine histological examination including acetylcholinesterase staining; specimens were thus classed as ganglionic or aganglionic.

RNA and DNA isolation

Total cellular RNA was extracted from tissues using Trizol (Life Technologies, Paisley, UK)¹¹. DNA was extracted using a QIAamp Tissue Kit (Qiagen Ltd, Crawley, UK) according to the manufacturer's instructions. RNA and DNA concentrations were determined by measuring the absorbance at 260 nm.

Mutational analysis of genomic DNA

Denaturing gradient gel electrophoresis analysis was carried out for all exons of the *EDNRB* and *EDN3* genes as described previously¹², and for all exons of the *RET* and *GDNF* genes. Polymerase chain reaction (PCR) products with aberrant bands were purified and sequenced as described previously¹³.

Reverse transcriptase-polymerase chain reaction

Single-stranded complementary DNA (cDNA) was synthesized from 5 µg total RNA using ribonuclease H⁻ reverse transcriptase (Superscript II; Life Technologies) according to the manufacturer's instructions.

Single-stranded cDNA was amplified by PCR using a DNA Thermal Cycler (Perkin Elmer Cetus, Foster City, California, USA), and products were detected as described

previously¹⁴. Primers were designed using GCG software (Wisconsin Genetics Group, Madison, Wisconsin, USA) for cDNA coding for *EDN3* (TGCTTCACCTAC-AAGGAC, AACCTTCCCTTCCTCTTC), *EDNRB* (TAAAGCAGAGACGGGAAG, CAGCAGCATAAGC-ATGAC) and glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*, GGTGAAGGTCGGAGTCAACGG, GGT-CATGAGTCCTTCCACGAT). The *EDN3* primers had no homology with the gene sequences for endothelin-1 or endothelin-2. All primers were supplied by PE-Applied Biosystems UK (Warrington, UK). PCR products were purified and sequenced to confirm reaction specificity (Applied Biosystems Model 373A, version 1.2.1).

Semiquantitative assay of *EDN3* and *EDNRB* messenger RNA levels by reverse transcriptase-polymerase chain reaction

The semiquantitative assay for *EDN3* and *EDNRB* has been described and validated previously¹⁴. Samples were removed from PCR reactions after 20, 25, 27, 30, 32 and 35 cycles to determine the range over which the PCR product increased in the exponential phase. Serial dilution curves using a standard reverse transcribed cDNA were obtained from duplex PCR reactions of either *EDN3* or *EDNRB* primer pairs together with *GAPDH* primer pairs. For each sample to be assayed, two PCR reactions using 1 and 2 µl cDNA were performed to show that the amount of product was proportional to the amount of cDNA used. Controls included omission of RNA from the reverse transcriptase (RT) reaction and omission of template from the PCR procedure.

Following agarose gel electrophoresis and photography, negatives were scanned using a laser densitometer (Molecular Dynamics, Sunnyvale, California, USA) using ImageQuant software (v3.3, 1992, Molecular Dynamics). GraphPad Prism (GraphPad Software, San Diego, California, USA) was used to produce standard curves, and from them to determine the relative amounts of cDNA in the diluted samples. The relative amounts of *EDN3* and *EDNRB* cDNA were expressed as a standardized ratio relative to the amount of the internal standard, *GAPDH*. The linearity of reverse transcription was confirmed by serially diluting control RNA and performing RT-PCR as described. Identical efficiencies of *EDN3* mRNA reverse transcription relative to that of *GAPDH* mRNA was shown by a graph of dilution *versus* standardized ratio.

Statistical analysis

The age distribution between groups was compared with the Mann-Whitney *U* test. Comparison of relative *EDN3*

and *EDNRB* steady-state mRNA levels between the ganglionic and aganglionic colon of patients with Hirschsprung disease was based on the paired Student *t* test. Comparison of relative mRNA levels between ganglionic, aganglionic and control colonic specimens was with one-way analysis of variance with Bonferroni correction. $P < 0.05$ was considered significant. All data were analysed using SPSS for Windows v6.1.2 (SPSS, Chicago, Illinois, USA) and GraphPad Prism software. Data are expressed as mean (s.e.m.) unless stated otherwise.

Results

Age matching

There was no significant difference in age distribution between the study and control groups. Median age was 3 (range 1–32) months in the study group and 3 (range 1–15) months in control children.

Mutational analysis

Two heterozygous coding sequence variants were detected in three of the ten patients. One patient had a Ser305Asn substitution in exon 4 of the *EDNRB* gene, and two unrelated patients had an identical InsA to Glu198X insertion in exon 4 of *EDN3*, leading to a premature stop in exon 5 at codon 198. No mutations in the coding regions of *RET* or *GDNF* were detected. One patient with Hirschsprung disease and the *EDN3* variant had total colonic aganglionosis, while the other had short-segment Hirschsprung disease, as had the patient carrying the *EDNRB* variant.

EDN3 and *EDNRB* messenger RNA expression

Bands of the predicted size for *EDN3* and *EDNRB* cDNAs (297 and 268 base pairs (bp) respectively) were found in all specimens of colon, including ganglionic and aganglionic segments of Hirschsprung disease gut. The expected size of *GAPDH* cDNA product (519 bp) was also obtained from all specimens. Sequencing confirmed the identity of each amplified cDNA. Thus *EDN3* and *EDNRB* mRNAs are expressed in normal (control) colon, and in both ganglionic and aganglionic Hirschsprung disease colon.

Semiquantitative reverse transcriptase-polymerase chain reaction assay standardization

Fig. 1 shows the products of exponential amplification of serially diluted cDNA for *EDN3* and *GAPDH*, together with the standard curve produced by densitometry of these bands (data for *EDNRB* not shown). When total RNA was

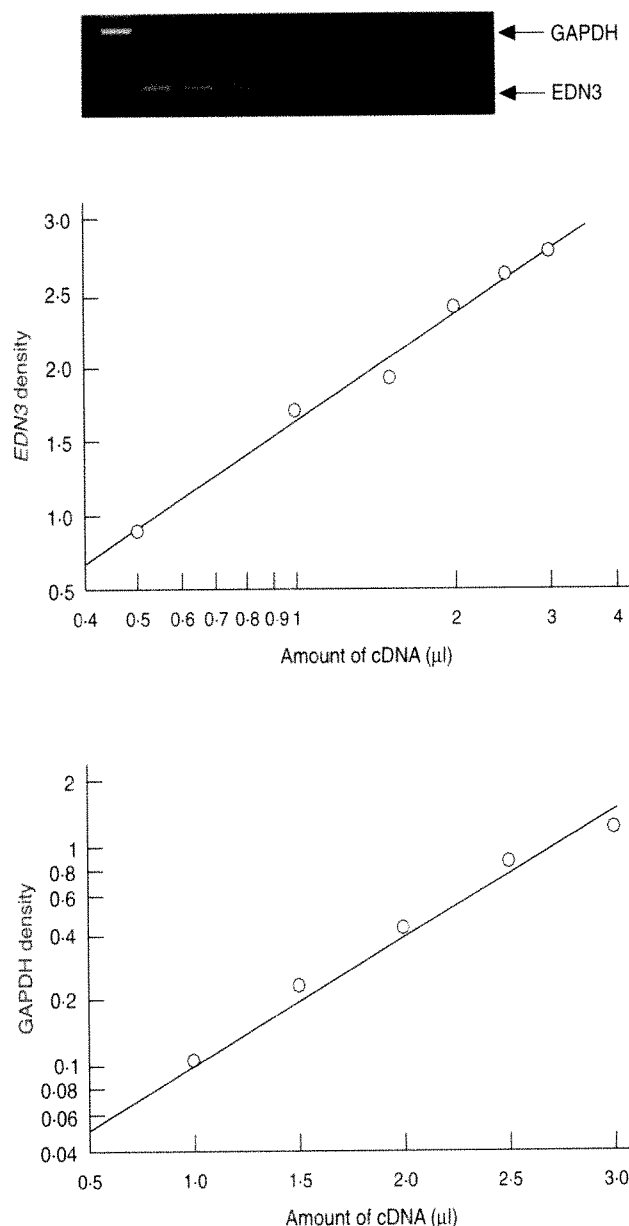


Fig. 1 Dilution curve used to standardize endothelin-3 (*EDN3*) ratios. GAPDH, glyceraldehyde 3-phosphate dehydrogenase; cDNA, complementary DNA

serially diluted and RT-PCR performed, linear regression analysis of amounts of product showed a linear relationship ($r^2 = 0.96$, $P < 0.02$) with a slope of 0.139 (Fig. 2). If the *EDN3*/*GAPDH* was independent of starting concentration of RNA, the ratio would be 1 with a gradient of zero. Thus, within the dilution range employed in the study, semiquantitative RT-PCR provided a good estimate of relative amounts of mRNA within specimens.

In the pooled data from the seven patients with Hirschsprung disease and no mutations in *EDN3* or

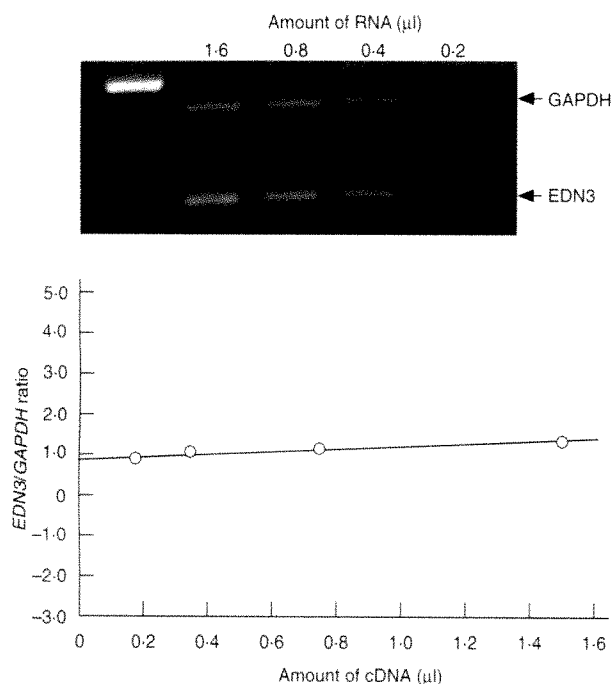


Fig. 2 Relationship of endothelin-3 (*EDN3*)/glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) reverse transcriptase-polymerase chain reaction product ratio to differing amounts of starting RNA. cDNA, complementary DNA

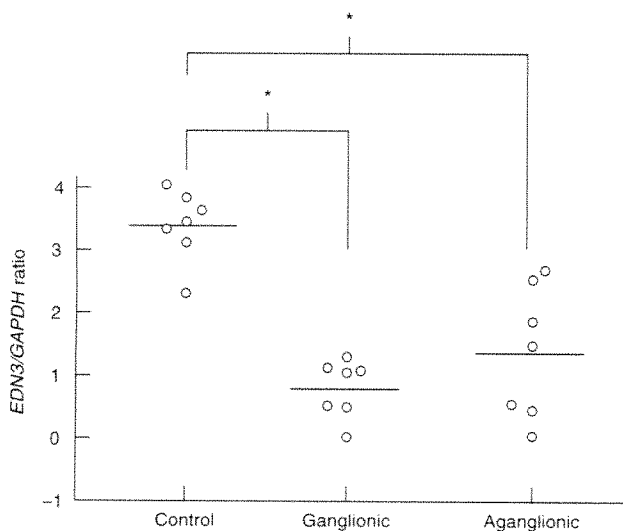


Fig. 3 Levels of endothelin-3 (*EDN3*) expression in ganglionic and aganglionic Hirschsprung disease colon, and in colon from control children. Bars represent mean *EDN3* messenger RNA (mRNA) levels standardized as a ratio to those of glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*). * $P = 0.01$ (one-way analysis of variance)

EDNRB, there was significantly less *EDN3* mRNA in both ganglionic (mean(s.e.m.) 0.94(0.50)) and aganglionic

(1.39(1.31)) gut specimens than in control specimens (3.38(0.33); $P = 0.011$) (Fig. 3). There was no significant difference in *EDN3* mRNA levels between ganglionic and aganglionic Hirschsprung disease segments.

In contrast to the differences in *EDN3* mRNA levels, there were no significant differences in mean(s.e.m.) *EDNRB* mRNA levels between ganglionic gut (2.33(2.66)), aganglionic gut (1.15(1.04)) or control specimens (0.83(0.38)). There was also no difference in *EDNRB* mRNA levels between paired ganglionic and aganglionic segments (paired *t* test).

Discussion

This study shows that *EDN3* and *EDNRB* mRNA transcripts are present in normal gut, and in ganglionic and aganglionic Hirschsprung disease gut. However, *EDN3* mRNA levels were significantly lower in both ganglionic and aganglionic sporadic Hirschsprung disease gut compared with those in controls. This reduced expression occurs in the absence of mutations in the exons of genes coding for either of the ET-3-ET-B or GDNF-Ret ligand-receptor systems. Thus, a transcriptional deficit in ET-3 may be the common factor leading to aganglionosis in this most common form of Hirschsprung disease.

The unexpectedly high number of *EDN3* and *EDNRB* sequence variants (three of ten) and lack of *RET* variants seen in this cohort of patients is in contrast to the previously published incidence of such variants in larger study populations^{10,15}. Since this was an unselected group of consecutive non-familial infants with Hirschsprung disease presenting to the authors' hospital, it may be that the background carriage rates of such *EDN3*-*EDNRB* variants in the north-west of England are higher. However, the genetic variants described here are not likely to be causative, for several reasons. The heterozygous insertion in the two patients with the *EDN3* sequence variant has also been reported in a patient with congenital central hypoventilation syndrome and there is evidence that the mature peptide can be produced in normal quantities despite the mutation¹⁶. The substitution mutation found in *EDNRB* has also been described previously¹⁷. However, of 100 patients with Hirschsprung disease screened in a more extensive study, this variant was found once in a sporadic patient and once in a familial case, where it did not segregate with the disease phenotype suggesting that it alone is insufficient to cause Hirschsprung disease (R.M.W.H., unpublished observations).

In the present study *EDN3* mRNA levels in Hirschsprung disease gut were approximately half those seen in control gut. This finding raises the possibility that this deficit may lead directly to distal aganglionosis. Recent *in situ*

hybridization studies in humans¹⁸ and mice¹⁹ have localized *EDN3* mRNA production to the embryonic gut mesenchyme before and during neural crest colonization of the colon. There is preliminary evidence to suggest that its *in vivo* role may be to prevent premature differentiation of migrating neuroblasts²⁰. A deficit in ET-3 would therefore result in premature differentiation within the colon and failure of colonization of the distal colon. In the few cases of Hirschsprung disease attributable to inactivating mutations in *EDN3*, the heterozygous state is sufficient to cause the Hirschsprung disease phenotype^{21,22}. Given that gene dosage is limiting, it would be expected that the reduced levels of *EDN3* mRNA measured here would also cause the Hirschsprung disease phenotype. If this were the case, identification of transcriptional regulators of *EDN3* expression should lead to delineation of further causative genes.

Given the mesenchymal origin of ET-3, it is not surprising that *in situ* hybridization studies have located *EDNRB* mRNA in neural crest cells in the fetal gut^{18,19,23}. However, a functional ET-B receptor has also been described in the smooth muscle of adult guinea-pig colon²⁴. The present finding of similar levels of *EDNRB* mRNA in both the ganglionic and the aganglionic gut also suggests that non-neural crest-derived gut cell populations such as smooth muscle express the ET-B receptor in the postnatal human.

Together with previous studies analysing the genetic basis of Hirschsprung disease, the present results indicate that a deficit in ET-3 levels may be a common step leading to aganglionosis in patients with short-segment Hirschsprung disease. In the more common sporadic form of the disease, the lack of correlation between known gene mutations and decreased *EDN3* expression points to an unknown factor(s) that acts by regulation of gene expression. In addition to *RET* and *GDNF*, other genes including *Sox10*, *Enx* and *Phox2b* are known to affect the innervation of the gut and hence may contribute to the Hirschsprung disease phenotype^{23,25-27}. It remains to be seen whether these gene products exert their effects by influencing levels of *EDN3* expression.

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Manometric assessment of an artificial bowel sphincter

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Background: This study investigated the relationship between functional clinical results after artificial bowel sphincter implantation and manometric assessment in 12 consecutive patients.

Methods: A postoperative manometric study was performed in 12 patients, including measurement of resting and squeeze pressures, opening characteristics and pressure during straining. The relationship between postoperative findings, clinical outcome and preoperative manometric data was investigated. Anal pressure after rectal distension with a closed cuff was studied in seven patients. Results were expressed as mean(s.d.).

Results: Continence for solid stool was achieved in all 12 patients. Five patients remained incontinent for gas. Anal resting pressure was 108(22) cmH₂O; there was no difference between continent and incontinent patients. Rectal distension induced anal relaxation in six of seven patients. Total duration of cuff opening was 113(8) s with an amplitude of 60(22) per cent; residual pressure was correlated with the preoperative resting pressure. The total duration of the opening phase in patients with defaecation difficulties (47(24) (range 0–65) s) was shorter than that in patients without defaecation difficulties (178(78) (range 100–320) s) ($P = 0.0022$).

Conclusion: Postoperative defaecation difficulties after implantation of an artificial bowel sphincter are related to a short duration of opening of the cuff. The anal sphincter played a role in postoperative resting anal pressures and allowed relaxation even if the cuff was closed.

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Introduction

Perianal implants of artificial bowel sphincters for severe anal incontinence appear to be promising for the management of severe anal incontinence. Many patients have normal continence for solid or liquid stools^{1–6} compatible with a normal social life. Evacuation difficulties occur in 20–45 per cent of patients who occasionally use small enemas to defaecate^{2,3,6}.

No correlation has been observed between postoperative anal canal pressure during activation and deactivation of the cuff and stool evacuation disorders^{2–6}. The aim of this study was to investigate the relationship between clinical data (anal incontinence and/or defaecation difficulties) and manometric assessment of the artificial sphincter in 12 consecutive patients who had had an artificial bowel sphincter implanted.

Patients and methods

Patients

Between September 1996 and September 1998, 12 artificial bowel sphincters were implanted consecutively after failure

of conventional treatment, in seven men and five women of mean age 51 (range 23–68) years. All had complete incontinence for solid and liquid stools with almost daily stool leakage owing to neurological disorders (seven patients), sequelae of anorectal surgery (two), obstetric trauma (one) and multiple associated causes (two). One patient had defaecation difficulties before implantation. Manometric assessment of anal function was performed before implantation. Informed consent for implantation was obtained from all patients, who were psychologically motivated and physically ready to use the artificial sphincter.

Surgical procedure

All patients were operated on by the same surgeon. The artificial sphincter used, as described previously³, was the Artificial Bowel Sphincter (Pfizer-American Medical Systems, Minneapolis, Minnesota, USA). The device includes three silastic components: an inflatable cuff (2–2.9 cm wide with lengths varying from 8 to 13 cm) placed in the perianal position, a pressure-regulating balloon in the laterovesical subperitoneal space, and an accessible control pump which is placed in the male scrotum or the female

labia majora. The surgical details of sphincter implantation have been reported previously³. After implantation, the artificial sphincter was deactivated with the control pump for 6 weeks, then the cuff was pressurized and the patient was taught to manipulate the control pump.

Manometric protocol

Manometric assessment of the artificial anal sphincter was performed with a rectosphincteric balloon probe as described previously⁷. The probe included three balloons, one distending the rectum and two others located 1 cm apart in the anal canal. The two anal balloons were filled with water. Rectal pressure was recorded with a perfused catheter with a hole located under the rectal balloon. The catheter was perfused with distilled water at a rate of 0.5 ml/min with a low-compliance pneumohydraulic capillary infusion system⁷. External pressure transducers (Statham P23XL; Spectromed, Bilthoven, The Netherlands) recorded pressures that were then stored and analysed on a computerized system. The manometric study protocol included closed and open cuff steps.

Closed cuff

The rectosphincteric balloon was inserted into the rectum and a pullthrough technique was used to assess the anal high-pressure zone. After probe placement, resting anal pressure was measured for 15 min. The highest pressure recorded in the anal canal was considered to be the resting pressure. The amplitude and duration of the voluntary anal contraction was determined by asking the patient to voluntarily contract the anal sphincter for as long as possible.

Open cuff

Patients were asked to manipulate the pump to empty the cuff. The time necessary to obtain residual pressure (opening time), the total duration, defined as the sum of the opening time and the refilling time, the residual anal pressure, defined as the lowest pressure observed during maximal relaxation, and the amplitude of the decrease in anal pressure as a percentage of basal pressure (Fig. 1) were recorded during two consecutive opening manipulations. Anal pressures were also studied as the subject strained as if to defaecate after placing the cuff in the deflated position.

Additional data

The rectoanal inhibitory reflex was elicited by distending the rectal balloon for 3 s with 50 ml of air. The components of the rectoanal inhibitory reflex were measured (i.e. total

duration, residual pressure, defined as the lowest pressure observed during maximal relaxation, and percentage relaxation, defined as the ratio between pressure at maximal relaxation and resting pressure). The rectoanal inhibitory reflex was investigated with a closed cuff in seven patients.

Clinical assessment after implantation

Patient satisfaction and functional assessment, including continence for liquid or solid stools or gas, failure and persistent incontinence or defaecation difficulties, were recorded at least 4 months after activation of the sphincter.

Statistical analysis

Results are expressed as mean(s.d.). Statistical analysis was performed with a non-parametric Mann-Whitney test for unpaired data and Wilcoxon test for paired data. The reproducibility of manometric data between two opening manipulations and the correlation of preoperative and postoperative resting pressures were assessed by linear regression. $P < 0.05$ was considered to be significant.

Results

Clinical assessment

After a mean follow-up of 16 (range 4–28) months, all 12 patients had normal continence for solid stools and eight for both liquid and solid stools. Five patients had permanent or

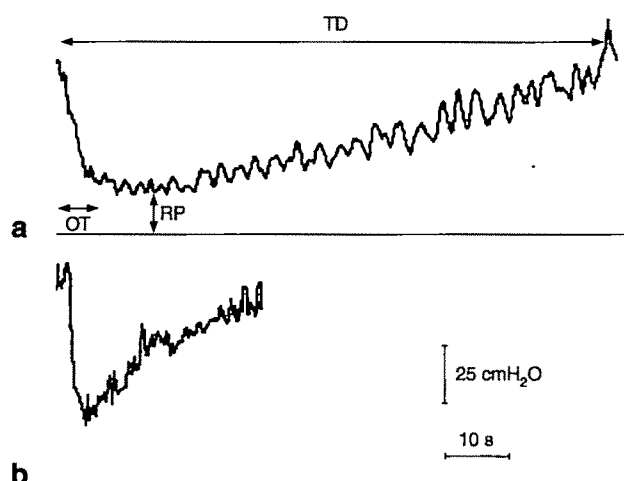


Fig. 1 Examples of deactivation of the artificial anal sphincter with its components residual pressure (RP), total duration (TD) (opening time and refilling time) and opening time (OT).

a Patient without defaecation difficulties.

b Patient with defaecation difficulties

intermittent incontinence primarily for gas. Evacuation difficulties occurred in six patients (three with gas incontinence) who had faecal impaction and needed to use intermittent small enemas to defaecate. One patient could not open the cuff and developed severe impaction. A biofeedback session was offered to this patient to teach her the effect of pump activation.

Manometric assessment of closed cuff

Anal resting pressure was 108(22) cmH₂O compared with 51(26) cmH₂O before artificial bowel sphincter implantation ($P < 0.001$). No difference was found in five patients with primarily gas incontinence after operation (106(27) cmH₂O) and seven others with normal continence for gas (110(20) cmH₂O) ($P = 0.87$).

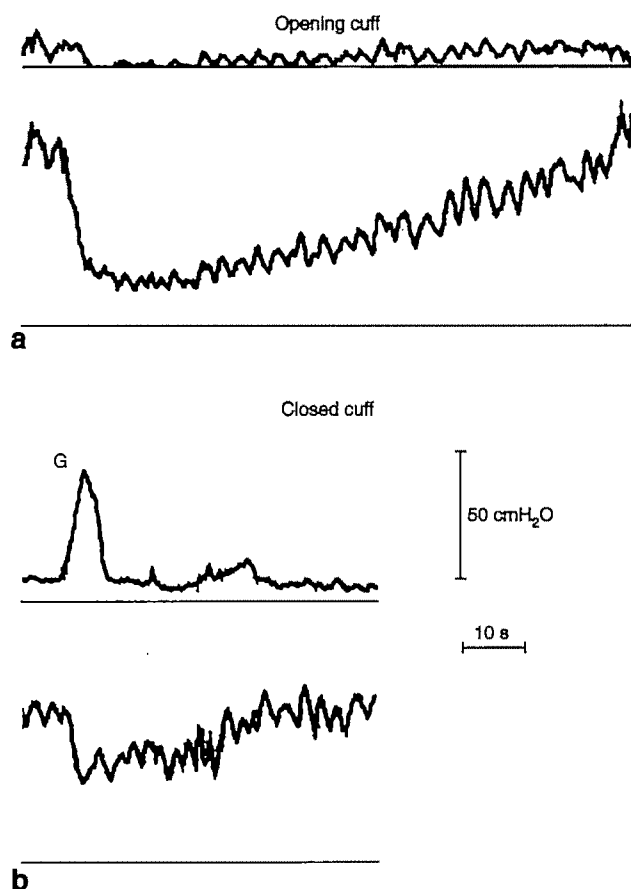


Fig. 2 a Deactivation of the artificial anal sphincter and b a spontaneous rectoanal inhibitory reflex observed in the same patient with a closed cuff and associated with transient perception of rectal gas (G). Recordings at rectal (upper trace) and anal (lower trace) sites are shown in each case

The rectoanal inhibitory reflex was observed spontaneously in one patient during the resting period and was associated with perception of gas in the rectum (Fig. 2). Seven subjects underwent one rectal distension of 50 ml with a closed cuff and a relaxation reflex was observed in six. This relaxation was characterized by a mean duration of 13(7)s, an amplitude of 30(16) per cent of the resting pressure and a residual minimal pressure of 75(17) cmH₂O.

The maximum amplitude (26(31) cmH₂O) and duration (18(20)s) of voluntary contractions were no different from those recorded before operation (26(23) cmH₂O and 19(13)s respectively).

Manometric assessment of cuff opening

The total duration of the first (113(8)s) and second (116(36)s) openings were correlated ($r = 0.94$, $P < 0.0001$). The amplitude of the first opening (60(22) per cent) and the second (52(71) per cent) were also correlated and reproducible in individuals ($r = 0.91$, $P = 0.0003$). The residual pressure after opening the artificial anal sphincter was correlated with the resting pressure recorded before implantation of the artificial sphincter ($r = 0.75$, $P = 0.018$).

The total duration of the opening phase in patients with defaecation difficulties (47(24) (range 0–65)s) was shorter than that in patients without such difficulties (178(78) (range 100–320)s) ($P = 0.0022$). The amplitude (54(27) per cent), residual pressure (48(32) cmH₂O) and opening time (10(5)s) in patients with defaecation difficulties were no different from those in patients without defaecation difficulties (63(10) per cent ($P = 0.69$), 33(12) cmH₂O ($P = 0.48$) and 19(7)s ($P = 0.10$) respectively). Cuff length tended to be shorter in six patients with defaecation difficulties (8, 10, 10, 10, 11, 12 cm) compared to patients without difficulties (9, 12, 12, 12, 12, 13 cm) ($P = 0.09$).

Increased anal pressure was observed during straining (after placing the cuff in the deflated position) in eight of 12 patients, four with and four without defaecation difficulties.

Discussion

The aim of this study was to assess manometric results in artificial anal sphincters. The artificial anal sphincter restored normal continence for solid stools in all 12 new patients, but did not restore continence to liquid in four and flatus in five patients, which confirms previous data^{2–6}. The magnitude of the mean high-pressure zone was similar to that reported by others⁵ and there were no differences between continent and incontinent patients after operation. This high-pressure zone results from the artificial sphincter and the patient's own sphincter. Indeed residual opening pressure was correlated with preoperative sphincter pres-

sure, which indirectly reinforces the participation of the patient's own sphincter in resting pressure. These results support a previous report by Lehur *et al.*⁶, which showed similar values of mean preoperative resting pressure and resting pressure with an open cuff.

As previously reported, the high-pressure zone was no different between continent patients and those incontinent for liquid and/or gas. A propagative contraction in the rectal ampulla and a decrease in pressure in the high-pressure zone was observed in one patient as he passed gas (Fig. 2). Because the cuff was closed this suggests that the decrease in pressure may have been due to relaxation of the patient's own anal sphincter. To confirm this hypothesis, the response of the high-pressure zone to rectal distension was studied in seven patients and a decrease in pressure similar to that seen during a rectoanal inhibitory reflex was observed. The position of the probe was checked to make sure it did not move up or down into the rectal ampulla. Because the cuff was closed, the decrease in pressure induced by rectal balloon distension could have been due to relaxation of the native anal sphincters in the six patients in whom the reflex was observed. The gas that passed through the anal canal in one patient and the decrease in pressure during rectal distension in the other six suggest an explanation for postoperative incontinence for gas without incontinence for solid stool. Gas incontinence might be due to relaxation of the patient's own sphincter. The level of residual pressure in the patient's own sphincter during spontaneous relaxation could be enough to prevent the solid stools, but not gas, from passing through the anus.

Five patients complained of defaecation difficulties at least 4 months after surgery. The amplitude and residual pressure during artificial sphincter opening were no different from those in six patients without defaecation difficulties. Simulated defaecation by abdominal straining was no different in patients with or without defaecation difficulties. The total duration of cuff deflation was shorter in patients with defaecation difficulties than in patients without and there were no overlaps in the two groups of patients. The opening time or the time needed to reach the minimal residual pressure during opening was no different in patients with or without defaecation difficulties. Thus, the difference in the duration of cuff deflation was only related to progressive reinflation of the cuff. Lehur *et al.*⁶ reported a patient who rapidly developed defaecation difficulties after implantation which were associated with such rapid cuff closure that the patient did not have enough time to defaecate. Manometric assessment of this patient showed a cuff closing time of 30 s to restore the high anal

pressure⁶. In the present series, no patient had a similar cuff closure time clinically and only manometric assessment suggested this dysfunction. Christiansen and Sparso² showed defaecation difficulties in two of ten patients, both with a 10-cm cuff. The present study used cuffs with lengths ranging from 8 to 13 cm and all patients with a 10-cm cuff had defaecation difficulties, although this was not statistically significant ($P = 0.09$) probably because of the small size of the two groups. These data suggest that choosing an appropriate artificial bowel sphincter length could help prevent defaecation difficulties. However, outlet obstruction constipation may be unmasked by restoring sphincter function to patients with severe faecal incontinence. Thus, these data do not completely confirm the cause of defaecation difficulties after artificial bowel sphincter implantation.

In conclusion, the clinical data in the present study confirm the efficacy of the artificial bowel sphincter in treating anal incontinence in 12 new patients. Manometric assessment of these patients suggests that defaecation difficulties may be due to the artificial bowel sphincter, particularly to a cuff that is too short, while persistent gas incontinence may result from relaxation of the patient's own anal sphincter.

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Quality of life after total colectomy with ileorectal anastomosis or proctocolectomy and ileal pouch–anal anastomosis for familial adenomatous polyposis

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Background: Knowledge of postoperative health status is important in decision-making about the type of operation necessary in patients with familial adenomatous polyposis (FAP). This study compared the quality of life (QoL) between patients with an ileorectal anastomosis (group 1) and those with an ileal pouch–anal anastomosis (group 2).

Methods: QoL was assessed with both a generic questionnaire (Short Form-36 Health Survey; SF-36) and a disease-specific questionnaire (European Organization for Research and Treatment of Cancer Colorectal QoL Questionnaire; EORTC QLQ-CR38). The SF-36 consists of 36 items representing eight generic health domains, and the EORTC QLQ-CR38 comprises 38 items representing disease-specific health domains. Both questionnaires were distributed among 323 patients with FAP known at the Dutch Polyposis Registry who had previously undergone either operation. The results of the SF-36 were compared with the scores of age- and sex-matched respondents from the general population.

Results: Some 279 patients (86 per cent), 161 in group 1 and 118 in group 2, completed the questionnaire. Generic and disease-specific QoL was the same for groups 1 and 2. The SF-36 scores of both groups were significantly lower than those of the general population.

Conclusion: There were no differences with respect to health status between patients in groups 1 and 2, and preference for either procedure cannot be based on QoL.

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Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disorder caused by germline mutations of the adenomatous polyposis coli (APC) gene. The disease is characterized by the development of hundreds of adenomatous polyps throughout the colon and rectum. Most patients develop polyps in the second and third decades of life; if left untreated, the patient eventually develops cancer by the age of 40 years¹. To date, the only effective therapy is prophylactic surgery.

Until recently the most frequently performed operation was total colectomy with ileorectal anastomosis². This procedure, which is technically relatively simple, has the advantage of a low complication rate and good functional results³. However, about half of these patients later require

proctectomy because of recurrent rectal polyps or rectal cancer. For this reason, an increasing number of patients are being treated with proctocolectomy and ileal pouch–anal anastomosis. This operation results in removal of all colorectal mucosa at risk, although there remains a risk of developing polyps at or in the ileal pouch^{4–6}. Besides this technique being more complex, it also has the incidental need for a temporary diverting ileostomy (and therefore a second operation), a higher complication rate, a risk of pouch excision due to malfunction, and the possibility of inferior functional results.

The fact that almost half of the patients who have undergone an ileorectal anastomosis need a secondary proctectomy⁷ might constitute a strong argument for the immediate choice of a proctocolectomy and an ileal pouch–anal anastomosis. Ileorectal anastomosis would be a more

appropriate procedure only if the resulting quality of life (QoL) were significantly better than that which followed proctocolectomy with an ileal pouch–anal anastomosis.

Most published studies on QoL in patients with FAP are characterized by small sample sizes and the use of non-standardized or non-validated questionnaires^{8–11}. Moreover, in only a few studies was QoL regarded as the principal outcome. In these studies the QoL following proctocolectomy and ileal pouch–anal anastomosis is most frequently reported as satisfactory or excellent^{3,9,12–15}, or very good, in comparison to that associated with a Koch pouch or a Brooke ileostomy^{16,17}. QoL in patients who underwent an ileorectal anastomosis is reported to be very good to excellent in 83–92 per cent of all patients^{3,12,13}. The present aim, therefore, was to assess the QoL with validated measures in a large series of patients with FAP having either an ileorectal anastomosis or a proctocolectomy and ileal pouch–anal anastomosis.

Patients and methods

In 1985 the Netherlands Foundation for the Detection of Hereditary Tumours established a registry of patients with FAP. By January 1997 the registry had collected medical and pathological data on 210 families, including 323 patients who had undergone surgery for FAP in various medical centres between 1961 and 1996. Colectomy and ileorectal anastomosis (group 1) was performed in 183 patients, whereas 140 patients underwent proctocolectomy and ileal pouch–anal anastomosis (group 2). In the Netherlands, proctocolectomy and ileal pouch–anal anastomosis had been performed in patients with FAP since 1984. A questionnaire was mailed to all registered patients.

An age- and sex-matched sample of 279 subjects was selected randomly from a group of volunteers from the general Dutch population ($n=1771$), who also completed the Medical Outcomes Study Short Form-36 Health Survey (SF-36)¹⁸. This group served as a control group.

Study instruments

The questionnaire included the Dutch version of the generic health-related QoL questionnaire (the SF-36¹⁹) and a disease-specific QoL instrument designed specifically for the evaluation of colonic cancer therapy (the European Organization for Research and Treatment of Cancer Colorectal Quality of Life Questionnaire; EORTC QLQ-CR38).

The SF-36 contains 36 questions, organized into eight multi-item scales: physical functioning, role limitations resulting from physical health problems, bodily pain, general health perception, vitality, social functioning, role

limitations resulting from emotional problems, and general mental health. In addition, the SF-36 has one single-item health transition, which estimates the change in health status over the preceding year²⁰. The SF-36 has previously been validated for use in postoperative patients²¹, and its reliability and validity have been established in both the USA^{22,23} and the Netherlands^{18,24}. The raw scores are linearly transformed to fit in a range from 0 to 100, with higher scores representing better levels of functioning.

The EORTC QLQ-CR38 is composed of 38 questions. Nineteen questions are completed by all patients, and the remaining 19 by subsamples of patients (men or women, or patients with or without a stoma). The EORTC QLQ-CR38 is subdivided into two functional scales (body image and sexual function), seven symptom scales (micturition problems, gastrointestinal tract symptoms, chemotherapy side-effects, defaecation problems, stoma-related problems, male and female sexual problems) and three single-item measures (sexual enjoyment, weight loss and future perspective). Validity and reliability have been established in Dutch patients with colorectal cancer²⁵. Scores are summed within scales and rescaled from 0 to 100. A higher score indicates better functioning for all functioning scales and for two of the single items, sexual enjoyment and future perspective. For all symptom scales and weight loss, a higher score indicates a higher level of symptomatology.

To correct for the possible confounding effects of co-morbid chronic conditions on QoL, respondents were asked whether their doctor had told them they had diabetes, renal or cardiovascular disease, chronic obstructive pulmonary disease, low back problems, arthritis, obesity or malignancy other than colorectal cancer.

Statistical analysis

For both subgroups, the SF-36 scales were compared with those for an age- and sex-matched sample of the general Dutch population¹⁸. Comparisons between groups were performed with univariate and multivariate analysis of variance. The effect of relevant covariates and their interactions were examined; these comprised sex, co-morbidity (i.e. at least one co-morbid chronic health condition), conversion of an ileorectal anastomosis to an ileal pouch–anal anastomosis, age, age at time of operation and length of follow-up. A subanalysis was performed to investigate the impact on QoL of the anastomotic technique (i.e. hand-sewn or stapled) used to construct an ileal pouch–anal anastomosis. $P<0.05$ was considered statistically significant. Incomplete questionnaires were handled in accordance with the standards indicated in the respective questionnaire manuals.

Results

The overall response rate was 86 per cent: 279 questionnaires were returned by 323 patients with FAP who had undergone operation. Of the 44 non-respondents, 22 patients had had an ileorectal anastomosis and 22 an ileal pouch–anal anastomosis. *Table 1* outlines the patient characteristics. Patients in group 1 were significantly older and had a longer follow-up period than those in group 2. Six patients from group 1 and eight from group 2 had a permanent ileostomy. In two of the six patients in group 1, an ileostomy was constructed following proctectomy for recurrence of polyps in the rectal remnant. An ileostomy was constructed in two other patients in group 1 because of

recurrent distal obstruction due to irresectable desmoid tumours. Two and five patients in groups 1 and 2 respectively had a permanent ileostomy because of anastomotic complications. Two patients from group 2 developed therapy-resistant pouch dysfunction and needed an ileostomy. In one patient from group 2 the mesenteric vessels were too short to allow an ileal pouch–anal anastomosis.

Questionnaire outcomes

The results derived from the SF-36 questionnaire are shown in *Table 2*. The multivariate analysis showed no differences between patients in groups 1 and 2 for all subscales ($F = 1.7$, 9 (number of variables), 266 (number of

Table 1 Patient characteristics

	IRA (group 1)	IPAA (group 2)	Non-responders		General population
			IRA	IPAA	
No. of patients	161	118	22	22	279
Response rate (%)	88	84			
Mean(s.d.) age (years)	41(15)	37(12)*	38(15)	37(11)	39(14)
Mean(s.d.) age at operation (years)	29(13)	30(11)	25(10)	26(12)	
Sex ratio (M:F)	77:84	67:51	13:9	17:5	142:137
Mean(s.d.) follow-up (years)	12.0(7.5)	6.8(4.9)*			
Type of anastomosis†					
Hand-sewn		45 (38)		14 (63)	
Double stapled		73 (62)		8 (37)	
No. of control endoscopies					
Median	1 every 6 months	1 every 12 months			
Range	6 per year to 1 every 3 years	3 per year to 1 every 5 years			
Co-morbidity‡	92 (57)	73 (62)		2 (9)	

*Values in parentheses are percentages. IRA, ileorectal anastomosis; IPAA, ileal pouch–anal anastomosis. * $P < 0.05$ (IRA *versus* IPAA, *t* test)

Table 2 Short Form-36 Health Survey results

	General population	IRA (group 1)	IPAA (group 2)	Difference between means (IRA – IPAA)*
Physical functioning	88.8(16.0)	56.3(13.8)	55.9(12.2)	0.5 (–2.7 to 3.6)
Role functioning: physical	82.4(31.4)	37.3(19.1)	35.3(19.4)	1.9 (–2.7 to 6.5)
Bodily pain	77.9(22.5)	37.2(7.7)	36.7(7.5)	0.4 (–1.4 to 2.3)
General health perceptions	74.6(18.8)	53.4(20.3)	52.7(20.4)	0.7 (–4.2 to 5.6)
Vitality	70.0(17.9)	55.2(19.8)	52.4(20.8)	2.8 (–2.0 to 7.7)
Social functioning	86.4(20.0)	67.4(18.1)	64.8(21.9)	2.6 (–2.1 to 7.3)
Role functioning: emotional	82.5(32.5)	39.2(18.3)	39.2(18.2)	0.01 (–4.4 to 4.4)
Mental health	77.6(16.7)	65.3(16.1)	63.7(18.3)	1.6 (–2.5 to 5.7)
Health transition	72.4(18.9)	50.0(17.3)	43.5(22.1)	6.5 (1.8–11.1)

Values are mean(s.d.); higher scores indicate better health status. *Values in parentheses are 95 per cent confidence intervals. IRA, ileorectal anastomosis; IPAA, ileal pouch–anal anastomosis

patients), $P=0.09$). The SF-36 scores for all subscales of patients in both groups were significantly poorer than those of the general population (group 1 *versus* general population, $F=111.9$, 9, 429, $P<0.001$; group 2 *versus* general population, $F=91.8$, 9, 385, $P<0.001$). The 95 per cent confidence interval (c.i.) from the difference in health transition means of the two surgical groups (1.8–11.1) seems to indicate a significant difference between both groups. However, the multivariate analysis was not significant; univariate differences were therefore not taken into account.

Mean scores and 95 per cent c.i. of the functional and symptom scales of the EORTC QLQ-CR38 for both patient groups are presented in Table 3. The multivariate analysis showed a significant difference between groups 1 and 2 ($F=2.3$, 7, 251, $P=0.03$). Univariate testing, however, showed that this effect was due only to the difference in defaecation problems ($F=6.3$, 1, 258, $P=0.01$). As expected, more defaecation problems were reported by patients from group 2 than from group 1.

Subanalyses

An additional subanalysis was performed to evaluate the impact of the difference in length of follow-up by comparing with group 2 a subset of 93 patients from group 1 who had the same length of follow-up as those in group 2. The analysis showed that there were no differences between these groups for the SF-36 subscales ($F=1.4$, 9, 207, $P=0.17$). The EORTC QLQ-CR38 subscales showed a

significant difference ($F=3.1$, 7, 207, $P=0.04$); however, univariate analysis showed again that this difference could be due to a single difference: more patients in group 2 had problems with defaecation ($F=10.9$, 1, 207, $P=0.01$).

A further subanalysis was performed between 44 patients from group 2 in whom the anastomosis was constructed with a double stapling technique and 71 patients in whom a hand-sewn anastomosis was constructed (in three patients the type of anastomosis was unknown). The multivariate analysis showed no differences between patients with either type of anastomosis for both SF-36 ($F=1.1$, 9, 115, $P=0.34$) and EORTC QLQ-CR38 ($F=1.0$, 7, 115, $P=0.47$) subscales.

Covariate analysis

Inclusion of sex, co-morbidity and conversion of an ileorectal anastomosis to an ileal pouch–anal anastomosis as covariates did not change the effects on both the SF-36 and EORTC QLQ-CR38 scores for groups 1 and 2. Moreover, although the groups differed in mean age and length of follow-up, a covariate analysis indicated that, for the SF-36, there was no interaction between the type of operation and age ($F=1.7$, 9, 276, $P=0.09$), age at time of operation ($F=1.6$, 9, 276, $P=0.10$) and follow-up ($F=1.2$, 9, 276, $P=0.31$). With regard to the EORTC QLQ-CR38 scores, inclusion of age and follow-up as covariates still resulted in a significant difference between the two groups; this was due to defaecation problems.

Table 3 European Organization for Research and Treatment of Cancer Colorectal Quality of Life Questionnaire functioning and symptom scales

	Scale*	IRA (group 1)	IPAA (group 2)	Difference between means (IRA – IPAA)†
Body image	F	87.5(21.9)	84.4(22.7)	3.1 (–2.2 to 8.5)
Sexual function	F	38.9(26.6)	42.2(26.3)	–3.3 (–9.8 to 3.2)
Sexual enjoyment	F	70.6(26.8)	67.5(31.0)	3.2 (–5.2 to 11.6)
Future perspective	F	70.5(31.7)	71.0(33.1)	–0.4 (–8.1 to 7.3)
Micturition problems	S	18.6(14.8)	20.5(16.0)	–1.9 (–5.6 to 1.8)
Gastrointestinal tract problems	S	21.4(20.2)	22.8(19.8)	–1.5 (–6.3 to 3.3)
Chemotherapy side-effects	S	11.2(15.6)	10.4(15.0)	0.8 (–2.9 to 4.5)
Defaecation problems	S	16.3(12.7)	20.6(15.0)	–4.4 (–7.8 to –1.0)‡
Stoma-related problems	S	27.9(34.6)	31.3(29.6)	–3.4 (–40.9 to 34.1)
Male sexual problems	S	15.7(27.4)	18.7(31.6)	–2.9 (–12.9 to 7.0)
Female sexual problems	S	12.4(20.0)	17.2(21.4)	–4.7 (–13.6 to 4.1)
Weight loss	S	9.1(20.4)	11.2(23.2)	–2.2 (–7.3 to 3.0)

Values are mean(s.d.) scores. †Values in parentheses are 95 per cent confidence intervals. *F indicates European Organization for Research and Treatment of Cancer Colorectal Quality of Life Questionnaire (EORTC QLQ)-CR38 functional scales and the single items of sexual enjoyment and future perspective results, with a higher score indicating better functioning; S denotes EORTC QLQ-CR38 symptom scales and the single item of weight loss, with a higher score indicating a higher level of symptomatology. IRA, ileorectal anastomosis; IPAA, ileal pouch–anal anastomosis. ‡ $P<0.05$ (group 1 *versus* group 2, MANOVA)

Discussion

Although several studies have shown that chemoprevention might be effective in reducing colorectal adenomas in patients with FAP, surgery is the only curative treatment available. Between their 15th and 30th years, most patients undergo prophylactic surgery consisting of total colectomy with ileorectal anastomosis or proctocolectomy and ileal pouch–anal anastomosis. During this key period of life, long-term relationships are established and career plans are made. Therefore, it is important to choose an operation that interferes as little as possible with normal life (i.e. a surgical procedure with a low complication rate, optimal functional results and no mortality). These requirements are also relevant when it is considered that these patients are usually asymptomatic.

It has been reported that patients with an ileorectal anastomosis have better functional results than those with an ileal pouch–anal anastomosis^{8,11}. In a previous study by the present authors it was observed that patients who had undergone total colectomy with a ileorectal anastomosis scored significantly better than those who had an ileal pouch–anal anastomosis with respect to daytime and nighttime stool frequency, soiling, occasional passive incontinence, flatus and faeces discrimination, stool consistency and the need for antidiarrhoeal medication²⁶. This might be a reason to choose total colectomy with ileorectal anastomosis as the primary treatment, although in almost half the patients it would be only a temporary solution. It is therefore important to know whether these better functional results also bring about an improvement in QoL.

As stated above, while several studies have been carried out on the QoL of patients with FAP undergoing either type of operation, none of these studies used standardized or validated questionnaires. Only one study with a small sample size, comprising 17 patients with an ileorectal anastomosis and seven patients with an ileal pouch–anal anastomosis, compared the QoL between patients with either operation and showed no significant difference between the two surgical procedures¹⁰.

The results of the present study of 279 patients with FAP demonstrate that, as measured by validated questionnaires, general and disease-specific QoL in patients with an ileorectal anastomosis is not different from the QoL of patients who have undergone proctectomy with an ileal pouch–anal anastomosis. The two groups were highly comparable except for age and duration of follow-up. Analysis of the impact of these factors and the effect of comorbidity or conversion of an ileorectal anastomosis to an ileal pouch–anal anastomosis indicated that they did not influence the results with respect to type of operation.

This is a rather surprising finding, as it might have been expected that, in view of the worse functional outcome reported, patients with FAP with an ileal pouch–anal anastomosis would score worse on QoL estimates^{8,11}. One explanation might be that the questionnaires measuring the QoL are not sensitive enough. However, the validity of the SF-36 and EORTC QLQ-CR38 questionnaires is demonstrated by their ability to discriminate between subgroups of patients who differ in clinical condition or performance status. For example, both questionnaires can differentiate between patients with a poor or good performance status, where poor performance status is defined as a Karnofsky performance score of 70 or less^{18,25}. Moreover, the large sample size of this study generated sufficient power to detect moderate to small differences in QoL. To estimate the capacity of the two questionnaires to detect small to moderate differences between ratings of patients with either an ileorectal or an ileal pouch–anal anastomosis, power calculation methods as described by Cohen²⁷ were used, where effect sizes of 0.20, 0.50 and 0.80 were considered small, medium and large respectively. The statistical power for both questionnaires to detect small differences was 0.72, and 0.99 to detect moderate and large differences. These arguments mean that these questionnaires were sensitive enough, and the sample size large enough, to pick up moderate to small differences in QoL between the two surgical procedures.

Another explanation for the relatively low QoL in patients with an ileorectal anastomosis might be that these patients need frequent endoscopic examinations and are in constant fear of a recurrence of polyps or cancer in their 'time bomb' rectum. Yet another explanation might be that follow-up of both patient groups is long enough to allow patients to become adjusted to the poor functional results of this procedure. All these patients might thereby have undergone a 'response shift'²⁸. This phenomenon is defined as a change in the meaning of a respondent's self-evaluation of QoL as a result of changes in their internal standards, values or conceptualization of QoL²⁹. In other words, patients may have lowered their internal standards, altered their values and changed their ideas about what constitutes a good QoL to accommodate deteriorating function. These changes may have been more pronounced among patients in group 2 than in group 1.

An unexpected finding of this study was that the QoL of patients with an ileorectal anastomosis was significantly poorer than that of the general population. This observation might be an argument for postponing the operation in patients with a mild phenotype of the disease. Such patients may be encountered in families with an attenuated or atypical form of polyposis.

On the basis of the results from this cross-sectional study, a difference in QoL cannot be used as an argument in the choice between total colectomy followed by ileorectal anastomosis, and proctocolectomy and ileal pouch–anal anastomosis. Rather, to obtain a valid assessment of short-term QoL and the experienced QoL in the course of time, a prospective study needs to be performed. Until such studies are available, the authors recommend proctocolectomy and ileal pouch–anal anastomosis for patients with FAP with a high risk of secondary surgery, and reserve total colectomy with ileorectal anastomosis only for patients with a low risk of secondary proctectomy.

The remaining problem is how to identify patients with a low risk of secondary proctectomy. It is reported that families with polyposis due to mutations located in a region on the APC gene between codons 1250 and 1462, especially mutations at codon 1309 or 1328, are predisposed to develop a severe phenotype and have a higher risk of rectal excision^{30,31}. Two recent studies have shown a high correlation between mutation site and the risk of secondary surgery^{7,31}. If these results are confirmed by studies with larger numbers of patients, this information might be useful in surgical decision-making.

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Intraoperative sentinel lymph node examination by imprint cytology and frozen sectioning during breast surgery

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Background: The purpose of the present study was to evaluate the usefulness of intraoperative imprint cytology and frozen sectioning of sentinel lymph nodes in patients with clinically node-negative breast cancer.

Methods: Sentinel node biopsy was performed in 101 patients with stage I or II breast cancer with clinically negative nodes using a dye-guided method. Intraoperative evaluation of sentinel node involvement by imprint cytology and frozen sectioning was compared with the final histopathological results of permanent sections. Tumour-negative nodes in paraffin sections stained by haematoxylin and eosin were further studied using an anticytokeratin antibody.

Results: The results of imprint cytology and frozen-section analysis were compared with those of haematoxylin and eosin-stained sections. The sensitivity, specificity and overall accuracy of imprint cytology were 96.0, 90.8 and 92.1 per cent respectively, and those of frozen-section examination were 52.0, 100 and 88.1 per cent. Ten sentinel nodes were tumour positive on imprint cytology and tumour negative on stained paraffin sections. Micrometastasis was found in eight of these nodes on immunohistochemistry. Taking these immunohistological results into consideration, the final sensitivity, specificity and overall accuracy of imprint cytology were 90.9, 98.5 and 96.0 per cent respectively.

Conclusion: Intraoperative imprint cytology is a useful method for evaluating the status of sentinel nodes and is more accurate than frozen-section analysis. In addition, imprint cytology can detect micrometastasis more accurately than conventional haematoxylin and eosin-stained sectioning.

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Introduction

Axillary lymph node dissection (ALND) is a standard operative procedure which provides precise staging and excellent local control in the treatment of patients with breast cancer^{1–8}. However, it is associated with considerable postoperative morbidity in a number of patients^{9–12}. The early postoperative complications are pain, numbness and paraesthesia of the upper arm as well as later motor dysfunction and lymphoedema of the arm. These complications often interfere with daily living and have a significant negative impact on a woman's ability to perform job-related activities.

Recently, sentinel lymph node biopsy has emerged as a promising procedure in the treatment of breast cancer¹³. The sentinel node is defined as the first axillary lymph node

draining the site of a primary tumour. Sentinel node biopsy has the potential to identify patients for whom ALND is unnecessary. Initial studies have proved that the status of the sentinel node is a reliable predictor of the status of the entire body of axillary nodes. It is expected that sentinel node biopsy will be a routine practice in the near future, replacing conventional ALND^{14–19}.

One of the most important issues with sentinel node biopsy is whether or not intraoperative evaluation of sentinel nodes can be performed with a high degree of accuracy. Accurate intraoperative examination of sentinel nodes would enable the selection of candidates for ALND during the initial operation, eliminating the need for second surgery in patients with false-negative results in the intraoperative sentinel node examination. The two techniques employed for intraoperative examination of sentinel

nodes are imprint cytology and frozen sectioning. Frozen sectioning is often used for intraoperative examination of sentinel nodes but this technique has the disadvantage that the sections may undergo artefactual changes, tissues are consumed, and the procedure is time consuming. On the other hand, imprint cytology can provide clear cytological detail and rapid diagnosis, preserving the tissue for permanent section. However, imprint cytology has the disadvantage that the number of cells examined is small and the chance of an indeterminate result is high²⁰.

The authors previously reported that sentinel nodes could be identified in 115 (76.7 per cent) of 150 patients using only indocyanine green dye²¹. There was concordance between sentinel node and axillary node status in 111 (96.5 per cent) of these patients. Moreover, in a recent report it was clarified that axillary node status, the presence or absence of lymphatic or vascular invasion in the tumour, and patient age affected success in identifying sentinel nodes²². The present study was undertaken to compare the usefulness of intraoperative examination of sentinel nodes by imprint cytology and frozen sectioning in patients with clinically node-negative breast cancer.

Patients and methods

One hundred and one patients with stage I or II breast cancer and clinically negative nodes were recruited consecutively to the study between December 1997 and April 1999. Patients with multiple primary tumours, non-palpable breast cancer, previous axillary surgery or pregnancy were excluded. Informed consent was obtained from all patients. Previous excisional biopsy had been performed in seven patients. The median age was 51 (range 28–75) years. The median pathological tumour size was 2.1 (range 0.7–5.0) cm. Twenty-two patients (21.8 per cent) had a mastectomy and 79 (78.2 per cent) had wide excision of the breast followed by complete ALND.

The technique of sentinel node biopsy used in this study involved injection of indocyanine green (Diagnogreen 0.5 per cent; Daiichi Pharmaceutical, Tokyo, Japan) and has been described previously^{21,22}. Blunt dissection was performed until a green-stained lymphatic tract and sentinel node were identified. After sentinel node biopsy, a level I and II ALND was carried out. Sentinel node and ALND specimens were submitted separately for pathological examination.

Sentinel nodes were serially sectioned at 2-mm intervals if they were 4 mm or more in diameter; they were bisected if they were less than 4 mm. Imprint cytological samples were made from all cut surfaces by touching to a glass slide and immediate fixation in 95 per cent ethanol. Slides were subjected to a Papanicolaou stain. The diagnostic categories

routinely used for cytology were negative, suspicious and malignant, but suspicious results were regarded as negative to help prevent false positives in the present study. After imprint cytology, a portion of the sentinel node was subjected to frozen sectioning. If there were several sentinel nodes per patient, a piece of the biggest node was submitted. Frozen sections were stained with haematoxylin and eosin. The remaining samples of sentinel nodes and non-sentinel nodes were fixed in neutral buffered formaldehyde and processed to paraffin blocks according to the standard procedure. One 4-µm section was cut from these blocks and stained with haematoxylin and eosin. One level of non-sentinel nodes was examined.

When the nodes were tumour negative in paraffin sections, an additional 4 µm section was cut and stained with immunohistochemical stain using the avidin-biotinylated peroxidase complex technique with mouse monoclonal antibody against cytokeratin (NCL-CK19; Novocastra Laboratories, Newcastle, UK).

Diagnostic accuracy, sensitivity and specificity were calculated using the definitions given by Greenberg²³.

Results

The mean number and size of sentinel nodes was 1.6 (range 1–6) and 11.0 (range 4.0–35.0) mm respectively. One hundred and fifty-eight sentinel nodes were identified from 101 patients. Cytological examination was performed in 153 sentinel nodes. Frozen sections were obtained from all patients. Thirty (19.6 per cent) of 153 nodes were judged to be tumour positive in paraffin sections, and 29 of these were cytologically positive. One hundred and twenty-three nodes were found to be tumour negative in paraffin sections, but metastasis was detected in ten of these nodes by cytological examination. The sensitivity, specificity and overall accuracy of imprint cytology were 96.7, 91.9 and 92.8 per cent respectively on a node basis (*Table 1*). When evaluating the cytological data on a patient basis, 25 patients (24.8 per cent) had at least one positive sentinel node in the paraffin sections. In 24 of these patients, imprint cytology of at least one sentinel node was positive. In seven of 76 patients with tumour-negative sentinel nodes in paraffin sections, the imprint cytology of at least one sentinel node was positive. Thus, the sensitivity, specificity and overall accuracy were 96.0, 90.8 and 92.1 per cent respectively on a patient basis (*Table 2*).

When evaluating the frozen-section data on a patient basis, the examination was positive in 13 of 25 patients with tumour-positive sentinel nodes in paraffin sections. There were no patients with tumour-positive frozen sections and tumour-negative paraffin sections. The sensitivity, specificity and overall accuracy of the frozen section examination

were 52.0, 100 and 88.1 per cent respectively on a patient basis.

There were ten sentinel nodes from seven patients that were tumour positive on imprint cytology and tumour negative on paraffin sections. Cytokeratin staining was performed on all of the sections. Micrometastasis, defined as a focus of metastasis 2 mm or less in largest dimension, was found in eight of these nodes (*Fig. 1*). Two of 113 nodes with tumour-negative imprint cytology and tumour-negative paraffin sections included micrometastases. Therefore, the final results of sensitivity were 92.5 per cent, specificity was 98.2 per cent and the overall accuracy was 96.7 per cent on a node basis (*Table 1*). When evaluating the data on a patient basis, micrometastasis was found in six of seven patients. The sensitivity was 90.9 per cent and the specificity 98.5 per cent. The overall accuracy of the imprint cytology on a patient basis was 96.0% (*Table 2*).

Table 1 Comparison of the results of imprint cytology of sentinel nodes with final histopathological diagnosis evaluated by haematoxylin and eosin staining and immunohistochemistry on a lymph node basis

	Final histopathological diagnosis			
	H & E alone		H & E and immuno-histochemistry	
	Positive	Negative	Positive	Negative
Imprint cytology				
Positive	29	10	37	2
Negative	1	113	3	111

H & E, haematoxylin and eosin

Table 2 Comparison of the results of imprint cytology of sentinel nodes with final histopathological diagnosis evaluated by haematoxylin and eosin staining and immunohistochemistry on a patient basis

	Final histopathological diagnosis			
	H & E alone		H & E and immuno-histochemistry	
	Positive	Negative	Positive	Negative
Imprint cytology				
Positive	24	7	30	1
Negative	1	69	3	67

H & E, haematoxylin and eosin

Discussion

Several reports have shown the results of the intraoperative assessment of sentinel nodes. Flett *et al.*²⁴ reported that frozen-section analysis of the sentinel node accurately predicted the axillary node status in 53 (95 per cent) of 56

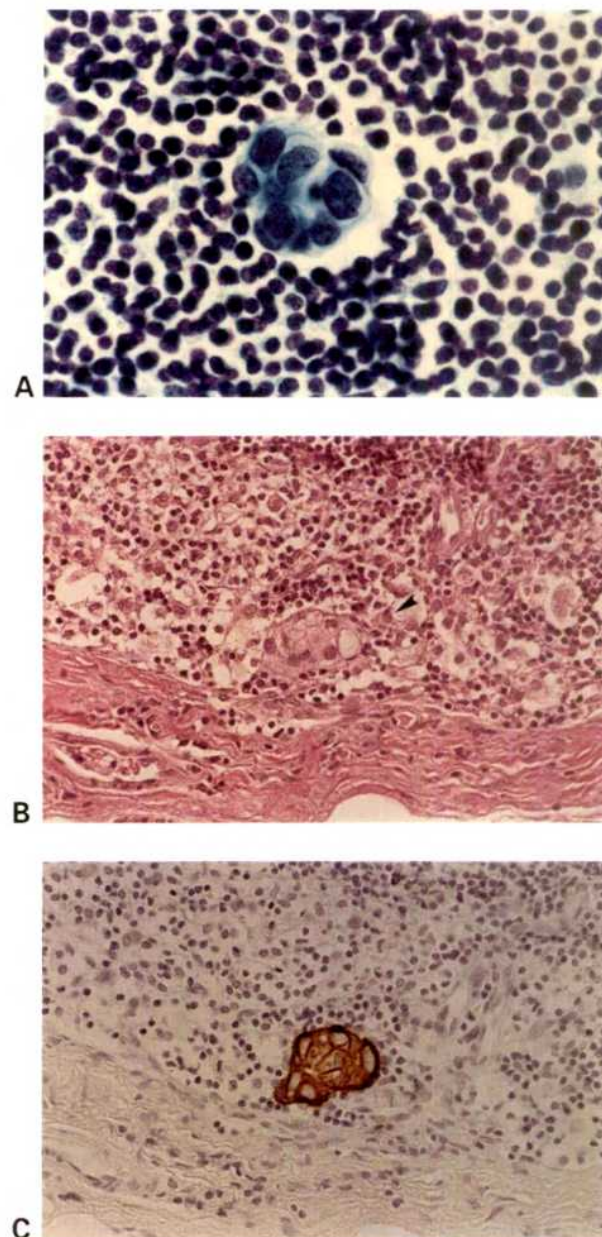


Fig. 1 a Example of tumour-positive imprint cytology (magnification $\times 400$).
b False tumour-negative haematoxylin and eosin stain; arrowhead indicates cancer cell nest (magnification $\times 200$).
c Tumour-positive immunohistochemical staining (magnification $\times 200$).

patients. van Diest *et al.*²⁵ reported that the sensitivity of frozen sectioning and imprint cytology per patient was 91 and 63 per cent respectively, and the specificity was 100 per cent for both methods. They concluded that intraoperative frozen-section analysis is a reliable procedure and that imprint cytology is significantly less sensitive than frozen sectioning. Veronesi *et al.*¹⁷ reported the results of frozen-section examination of sentinel nodes with an accuracy of 83 per cent; however, the false-negative rate was sufficiently high (17 per cent) to cause concern. In a more recent report Veronesi *et al.*²⁶ described a new intensive method that examines some 30 sections of the sentinel node with additional evaluation of the same number of sections by immunohistology if the haematoxylin and eosin staining is negative. This new method was reported to provide an acceptable false-negative rate (5.5 per cent) for use as a basis for deciding whether or not to perform ALND. Bloustein and Silverberg²⁷ mentioned that nodes containing metastatic carcinoma can usually be easily diagnosed by the imprint method. Rubio *et al.*²⁸ reported the results of imprint cytological examination of sentinel nodes, with 99 per cent accuracy and a 1 per cent false-negative rate on a sentinel node basis, and 98 per cent accuracy and a 3 per cent false-negative rate on a patient basis. Ratanawichitrasin *et al.*²⁹ reported that imprint cytology of the sentinel node accurately predicted the status in 52 (95 per cent) of 55 patients. They emphasized that imprint cytology is a simple, quick and accurate method for detecting sentinel node involvement.

In this study the overall accuracy of the imprint cytology was 92.1 per cent on a patient basis. Furthermore, imprint cytology can detect micrometastasis more precisely than final paraffin sections evaluated by haematoxylin and eosin staining, since almost all the nodes that were evaluated as negative by routine haematoxylin and eosin staining but positive by imprint cytology were in fact positive on immunohistochemical examination. Imprint cytology may provide the ability to identify micrometastases that are too small to be detected by haematoxylin and eosin paraffin sectioning. Taking these immunohistological results into consideration, the final sensitivity, specificity and overall accuracy of imprint cytology on a patient basis were 90.9, 98.5 and 96.0 per cent respectively. Imprint cytology can accurately evaluate the status of sentinel node involvement. On the other hand, the overall accuracy of the frozen sectioning per patient was 88.1 per cent. This procedure seems to be unsuitable for the intraoperative detection of sentinel node involvement because of its low sensitivity.

In conclusion, intraoperative imprint cytology is a useful method for evaluating the status of sentinel node and thus for making a decision regarding ALND. In addition, imprint cytology can detect micrometastasis more sensi-

tively than conventional haematoxylin and eosin paraffin sectioning.

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Gunshot injuries of the popliteal artery

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Background: Guidelines for the management of popliteal artery trauma emanate mainly from military experience. This study was undertaken to describe the management of popliteal injuries in a civilian vascular surgical unit with a large trauma workload.

Methods: A retrospective review of records of patients treated between 1983 and 1997 was undertaken.

Results: Some 117 popliteal artery gunshot injuries were treated (83 low velocity, 16 high velocity, 18 shotgun). Associated fractures occurred in 44 patients and 40 had popliteal vein injuries. Treatment of the arterial injury included vein graft interposition in 71, primary reanastomosis in 19, prosthetic graft interposition in four, lateral suture in one, vein patch in one and ligation in one patient; 84 fasciotomies were performed. No perioperative deaths occurred. There were 20 primary and 14 secondary amputations. Factors associated with amputation were high-velocity injuries, delay in revascularization in excess of 7 h, arterial transection, associated fracture, and compartment syndrome or muscle infarction.

Conclusion: Civilian popliteal gunshot injuries are attended by a high amputation rate. Prompt resuscitation and revascularization appear to be the only correctable factors that may improve limb salvage rates.

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Introduction

Numerous authors have recognized that injury to the popliteal artery has a relatively poor outcome compared with other lower limb vessel injuries. Most series of significant size contain a preponderance of injuries due to blunt trauma^{1–5}. Although several series describing popliteal injuries from penetrating trauma have been published, current practice in the management of this problem is largely guided by reports detailing the military experience^{6–10}. The high rate of interpersonal violence in South Africa and the increasing frequency of firearm injuries¹¹ has given surgeons here an exceptional exposure to the management of popliteal artery gunshot wounds in a civilian environment. The present study reviews a single-centre experience of popliteal artery gunshot wounds in a civilian practice.

Patients and methods

The Metropolitan Vascular Service provides a vascular referral service for the greater Durban area and for most of

the province of Kwa-Zulu Natal. All elective peripheral arterial surgery and most emergency arterial surgery is performed by the unit in one tertiary and one secondary hospital in Durban. The Service has a catchment area with an estimated population of 8 million and is the sole provider of state-sponsored vascular care. All patients treated by the service are recorded prospectively on a computerized database. Patients with a popliteal artery injury who were seen between 1983 and 1997 were traced. Data extracted from summaries and clinical case notes were entered on to a separate database (FileMaker Pro 3.0; Claris, Santa Clara, California, USA).

The statistical significance of the association between outcome and severity of injury or treatment was assessed using χ^2 analysis and Fisher's exact test in cases in which the cell size or difference was 5 or less. $P < 0.05$ was considered significant.

During this 15-year interval 260 patients with a popliteal artery injury were treated. One hundred and seventeen of these injuries were due to gunshot wounds, 125 to blunt trauma and 18 to stab wounds. Patients with clinically

obvious arterial injuries were taken to the operating theatre without preliminary angiography. Direct angiography was performed on table before exploration when the level of injury was uncertain. Where vascular injury was suspected but not obvious and no limb threat existed, formal angiography was performed in the radiography suite. The medial approach to the popliteal artery was preferred where surgery was necessary. Rapid control and wide exposure was afforded by division of the pes anserinus, which was reattached to the periosteum overlying the tibial condyle at the end of the procedure. This approach also facilitated distal extension of the incision if fasciotomy was indicated.

Heparin was instilled locally and no patient received systemic anticoagulation. Arterial repair was performed according to standard practice. Fasciotomy was the initial procedure in patients with clinical evidence of compartment syndrome. This assessment was made clinically, on the basis of increased muscle turgor; compartment pressures were not measured. Where muscle infarction in more than two calf compartments was found, primary amputation was performed and no revascularization was attempted.

Presenting features

Men accounted for 109 patients (93 per cent). They were generally young and otherwise fit, with a median age of 24 (range 13–60) years. These findings were in keeping with the demographic profile of victims of interpersonal violence in South Africa. Inadequate clinical assessment at primary hospitals (22 per cent) combined with ineffective transportation (39 per cent) frequently resulted in late referral to the vascular service and subsequent delays in operative intervention. Only 37 patients (32 per cent) had surgery within 6 h of sustaining the gunshot wound. A total of 100 patients presented within 48 h, with a mean delay of 12 h. Eight patients were seen between 2 and 7 days following injury and nine presented more than 7 days after being injured. The greatest delay was seen in a patient who presented with a slowly expanding popliteal fossa haematoma 7 months after sustaining a low-velocity gunshot injury.

Low-velocity firearms caused the wounds in 83 patients (71 per cent), 18 injuries (15 per cent) arose from shotgun wounds and 16 (14 per cent) from high-velocity gunshot wounds. The proximal popliteal artery above the knee was involved in 55 injuries (47 per cent) and the distal segment in 62 (53 per cent). The type of injury was transection of the artery in 62 patients (53 per cent), lateral perforation in 39 (33 per cent), thrombosis due to proximity percussion injury in ten (9 per cent), spasm in three (3 per cent) and unknown in three (3 per cent).

Forty patients (34 per cent) had associated venous injuries, these being complete transection in 16 and lateral

perforation in 24. There were associated fractures in 44 patients (38 per cent). Twelve patients had both venous injury and fracture. Six patients (5 per cent) were documented to have sciatic or tibial nerve injuries. Seven patients had associated injury remote to the leg.

Eleven patients were actively bleeding at presentation. Twelve were shocked with a systolic blood pressure less than 100 mmHg. The mean (s.d.) haemoglobin concentration was 9.9(2.7) (range 4–16) g/dl. Forty-three patients had a haemoglobin level below 10 g/dl. Sixty-eight patients (58 per cent) had clinical evidence of raised calf compartment pressure. Movement at the ankle and toes was recorded as normal in 47 patients (46 per cent), diminished in 33 (32 per cent) and absent in 25 (24 per cent). Sensation was preserved in 49 legs (47 per cent), diminished in 30 (29 per cent) and absent in 24 (23 per cent). Compartment syndrome was more frequent when fractures were present, occurring in 34 of 44 patients compared with 37 of 73 who had no bony injury (postoperative compartment syndrome included) ($P=0.03$).

Treatment

All patients were treated surgically. Procedures performed on 97 arteries are listed in *Table 1*. Venous injuries were repaired by lateral venorrhaphy in 19 patients and by end-to-end anastomosis in one. The remaining 20 patients had the venous injuries ligated. No complex venous repairs were undertaken. The practice was to ligate veins where lateral repair or end-to-end repair was impossible. Eight fractures were fixed internally and a further eight had external fixators applied. The remaining patients had the fractures reduced and immobilized with a plaster backslab while awaiting definitive orthopaedic intervention.

Four-compartment open fasciotomy using medial and lateral calf incisions was performed in 84 legs (72 per cent).

Table 1 Secondary amputation rate according to the method of treatment for popliteal artery injury

Procedure	No.	Secondary amputation
Reversed saphenous vein interposition graft	71	11 (15)
End-to-end anastomosis	19	2 (11)
Prosthetic interposition graft	4	1 (25)
Lateral suture	1	0
Saphenous vein patch	1	0
Ligation	1	0
Total	97	14 (14)

Values in parentheses are percentages. There were no significant differences between repairs (χ^2 test).

The indications were clinical signs of compartment syndrome in 60 legs (71 per cent), but fasciotomy was prophylactic in 24 (29 per cent). Fasciotomy was considered necessary when there were combined arterial and venous injuries, or when adequate clinical assessment of compartments was not possible (nerve injury, head injury, need for postoperative paralysis or sedation for ventilation). The lack of any muscular contraction in response to mechanical or electrical stimulation, or the presence of obvious muscle necrosis was considered to be an indication of irreversible muscle ischaemia. Muscles were viable in 48 patients (57 per cent) and frankly non-viable in 20 (24 per cent). Three of these had involvement of up to two calf compartments, while 17 had irreversible ischaemia of three or more compartments. Viability was assessed as doubtful in 16 patients (19 per cent). When irreversible muscle ischaemia involved more than two of the four calf compartments, revascularization was not attempted and an amputation was performed. On this basis, 20 primary amputations were done, all above the knee.

Results

There were no perioperative deaths. The median hospital stay was 30 (range 4–183) days. Eighty-one patients (69 per cent) made an uneventful recovery. Complications in the remaining patients are listed in *Table 2*. The early arterial/graft occlusion rate (within 30 days) was 12 per cent. These failures were thought to be due mainly to technical errors in repair. Ten of the occlusions affected a reversed saphenous vein graft, while two end-to-end anastomoses blocked. There were no significant differences between the occlusion rates related to different methods of arterial repair. All of the patients who were found to have necrotic muscle after operation had been subjected to fasciotomy at the initial operation. Nine were noted to have muscle of doubtful viability, which was left alone, one had muscle assessed as viable at initial operation (fasciotomy) and one had a single infarcted compartment excised. Four patients developed

myoglobinuria, all of whom presented with compartment syndrome, and had therapeutic fasciotomy. Three had muscle of doubtful viability and one had excision of two infarcted compartments. Of the 16 patients thought to have muscle of doubtful viability, seven had the leg salvaged (two required orthotic support for persistent foot-drop; the remainder had no residual functional deficit) as a result of a deferred decision regarding amputation. Although three patients developed transient renal dysfunction from reperfusion syndrome, there were no lasting systemic sequelae or deaths associated with secondary amputation in this group. Persistent foot-drop was attributed to primary nerve injury in three patients and to the late effects of compartment syndrome in 14.

There were 14 secondary amputations giving an overall total of 34 amputations. Indications were graft occlusion with a non-viable leg in six patients, dead muscle despite patent arterial repair in five, flail and insensate leg after nerve injury in two and gas gangrene in one. The overall 30-day limb salvage rate was 71 per cent. Popliteal injuries due to blunt trauma encountered in the same period resulted in a mortality rate of 3 per cent and a limb salvage rate of 69 per cent.

Factors associated with amputation are enumerated in *Table 3*. High-velocity gunshot injuries were associated with a higher amputation rate than low-velocity ($P=0.006$) or shotgun ($P=0.09$) wounds. Increasing delay was associated with a poor outcome, with statistical significance being reached at 7 h. Compartment syndrome was associated with a highly significantly increased risk of amputation, as was limb fracture. Surprisingly, concomitant venous injury was not associated with a higher amputation rate. The secondary amputation rate was higher in patients treated by venous ligation ($n=3$; 15 per cent) than for those who had venous repairs ($n=1$; 5 per cent). The combined secondary amputation rate in patients with no venous injury and those with venous repair was 30 per cent ($n=29$). This was not significantly different from that in patients with venous ligation ($P=0.3$), confirming that ligation did not worsen outcome. The association between extensive muscle compartment infarction and amputation was to be expected, as policy indicated ablation when more than two compartments were non-viable.

Table 2 Complications following popliteal artery repair (36 patients)

	No.
Graft occlusion	12
Muscle necrosis	11
Myoglobinuria	4
Superficial wound sepsis	4
Causalgia	1
Postoperative compartment syndrome	3
Foot-drop	17

Discussion

Popliteal artery injuries remain a challenge for the vascular surgeon, and result in a disproportionate rate of leg loss or dysfunction. Most series of popliteal artery gunshot wounds originate from the military sector^{5–10}. Civilian series contain a majority of blunt injuries, which appear to carry a worse prognosis^{3,11}. Barros D'Sa has described a sizeable series of

Table 3 Factors associated with amputation (total 117 patients)

	Amputation			Limb salvage	P†
	Primary	Secondary	Combined		
Type of weapon					
Low velocity	12 (14)	10 (12)	22 (27)	61 (73)	0.006
High velocity	6 (38)	2 (12)	8 (50)	8 (50)	
Shotgun	2 (11)	2 (11)	4 (22)	14 (78)	
Delay*					0.007
< 7 h	2 (5)	5 (12)	7 (16)	36 (84)	0.007
> 7 h	8 (14)	17 (30)	25 (44)	32 (56)	
Shock	1 (8)	2 (17)	3 (25)	9 (75)	
Location					
Above knee	10 (18)	4 (7)	14 (25)	41 (75)	0.004
Below knee	10 (16)	10 (16)	20 (32)	42 (68)	
Arterial pathology					
Transection	17 (27)	10 (16)	27 (44)	35 (56)	0.004
Lateral perforation	0	3 (8)	3 (8)	36 (92)	
Thrombosis/intimal tear	0	1 (10)	1 (10)	9 (90)	
Active haemorrhage	1 (9)	4 (36)	5 (45)	6 (55)	< 10 ⁻⁸
Haemoglobin < 10g/dl	12 (28)	8 (19)	20 (47)	23 (53)	
Compartment syndrome	20 (29)	13 (19)	33 (49)	35 (51)	
Associated injury					
Vein	2 (5)	4 (10)	6 (15)	34 (85)	0.012
Fracture	11 (25)	10 (23)	21 (48)	23 (52)	
Non-viable calf muscle‡					
None	0	4 (8)	4 (8)	44 (92)	0.012
1–2 compartments	0	0	0	0	
3–4 compartments	18 (100)	0	18 (100)	0	
Doubtful	0	9 (56)	9 (56)	7 (44)	

Values in parentheses are percentages *Patients presenting after 48 h are excluded † χ^2 test, ‡P values not shown when greater than 0.05

popliteal artery injuries due to punitive 'knee-capping'^{12,13}. South African surgeons face a large workload relating to penetrating trauma and a trend toward more frequent firearm than stab injuries has been demonstrated¹⁴.

The need for surgical exploration of penetrating wounds of the popliteal fossa with clear evidence of vascular trauma is widely recognized. Controversy exists regarding the management of patients with penetrating proximity extremity trauma and 'soft' or no signs of arterial injury¹⁵. The yield from routine angiography varies between 10 per cent¹⁶ and 24 per cent¹⁷, reflecting differences in the definition of 'proximity', and in the policy regarding management of patients with an abnormal angiogram. The policy adopted in the authors' unit entailed prompt surgical exploration when clear signs of a vascular injury existed. Preliminary angiography (usually direct angiography in the operating room) was performed when multiple potential sites of injury were present, such as multiple gunshot wounds, shotgun injuries or a wound tracking along the axis of the leg in proximity to the artery. Formal angiography was reserved for patients with 'soft' signs, such as non-pulsatile haematoma or a history of transient pulse deficit.

The procedure of choice for popliteal artery trauma is repair without resort to prosthetic grafts. Where vein grafts are required, saphenous vein from the groin of the contralateral limb is preferred. Vein harvest from the affected limb should be avoided to minimize further compromise to venous drainage. It may, however, be necessary when contralateral long saphenous vein is unavailable or unsuitable. Limb salvage rates for all types of arterial repair were comparable in this study, but the small number of prosthetic grafts precluded meaningful comparison with vein grafts.

Proponents of formal venous reconstruction claim improved early and late results^{18,19}. Based on an analysis of pooled experience derived from the Vietnam Vascular Registry, Rich *et al.*⁶ have advocated an aggressive approach towards venous repair. However, some of the late results of complex venous reconstruction are disappointing; panel and spiral grafts have a 30-day patency rate of only 50 per cent²⁰. Bermudez *et al.*²¹ showed that most patients with lower extremity venous injuries developed late chronic venous insufficiency after both ligation and repair. Functional disturbance was maximal in those who had complex venous repairs or fasciotomy.

The place of fasciotomy in the management of lower extremity vascular trauma continues to evoke debate. Several authors credit liberal and extensive fasciotomy as a major factor contributing to the successful management of popliteal injuries^{4,22}. In contrast, Abouezzi *et al.*²³ reappraised the indications for fasciotomy and concluded that neither combined vascular injury nor the need for venous ligation necessitated fasciotomy. However, the indication for fasciotomy is recognized as being greatest after popliteal vessel trauma (62 per cent). The morbidity of 'unnecessary' fasciotomy (where muscle swelling is absent or minimal and the muscle can usually be closed early) is minimal, and is exceeded by the consequences of untreated compartment syndrome. Liberal and adequate fasciotomy is therefore strongly advocated.

Where injuries required multidisciplinary involvement, priority was awarded to revascularization. Orthopaedic manipulation or fixation may then follow in an unhurried fashion. Careful reappraisal of the repair and limb perfusion thereafter is mandatory. Temporary arterial shunting has been advocated for complex injuries for which fracture fixation or extensive debridement is indicated^{12,13,24,25}. Shunt placement, however, requires dissection and control of the injured vessel. In this experience, definitive vascular repair added little delay after control of the injured vessel had been achieved. The preferential use of external fixators and backslabs limits the risk of compromise to the vascular repair during manipulation and internal fixation.

Deficiencies in primary health care provision and interhospital transport create a situation analogous to that of military conflict. Definitive management is often delayed. The importance of prolonged ischaemia as a significant risk factor for limb loss must be emphasized. In part, Barros D'Sa's commendable limb salvage rates may be attributed to the fact that 87 per cent of patients were admitted within 1 h of being shot¹². Most factors associated with amputation were related to the severity of the initial injury or degree of ischaemia. Findings in the present study were similar to those published previously^{4,8,19,26,27}, except for the lack of effect of venous injury or ligation on outcome. Prompt resuscitation and revascularization surgery appear to be the only correctable factors that may improve the rate of limb salvage.

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Surgical management of intra-abdominal desmoid tumours

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Background: Intra-abdominal desmoids are uncommon neoplasms. The aggressive nature of these tumours and the potential for major morbidity secondary to resection can present a difficult surgical dilemma.

Methods: Patients with histologically confirmed intra-abdominal desmoid tumours undergoing laparotomy were identified from a prospective database. Clinical features and outcomes in this group were evaluated.

Results: The study group comprised 24 patients. Sixteen patients underwent complete resection of the tumour while eight had biopsy only, with or without intestinal bypass. Small intestinal resection was performed in 12 patients, including three who had a near-total enterectomy. Median follow-up was 62 months, with an actuarial overall survival rate of 73 per cent at 10 years. There was no difference in survival rate between completely resected and unresected patients ($P=0.73$). There were seven deaths in the entire group, of which four were in those undergoing complete resection.

Conclusion: Operation can cure patients with intra-abdominal desmoid tumours, but may result in significant morbidity, especially from loss of small intestine. No other therapy is a predictably good alternative to operation but the natural history of desmoids is often characterized by prolonged periods of stability or even regression. A period of watchful waiting, until significant symptoms develop, may be the most appropriate course in patients who risk mesenteric vascular injury or substantial enterectomy with attempts at resection.

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Introduction

Intra-abdominal desmoid tumours occur sporadically¹ or in association with familial adenomatous polyposis (FAP)² and often present a clinical dilemma. The tumour is also designated in the literature as mesenteric fibromatosis. These tumours exhibit benign histological features and do not metastasize, yet their local behaviour is aggressive as they invade contiguous structures and have a marked propensity to recur after resection³. Intra-abdominal desmoids are frequently associated with the intestinal mesentery, a feature that predisposes to complications of bowel obstruction and fistula formation, and also impedes efforts at resection.

The enigmatic biology and anatomical location of intra-abdominal desmoids make treatment recommendations difficult; no therapy is predictably efficacious and mixed results have been reported. Non-operative therapies have been tested and small series have documented regression following therapy with antioestrogens (tamoxifen, toremifene)^{4,5}, non-steroidal agents, cytotoxic chemotherapy⁶ and radiotherapy^{2,7}. However, there are also reports of spontaneous regression, making the role of medical therapy unclear^{1,5}. Some authors have recommended an aggressive surgical approach aimed at wide excision^{1,8,9}, while others advocate a less radical strategy².

The purpose of this report is to assess the outcome of a group of patients with surgically managed intra-abdominal desmoids. Although Burke *et al.*³ reported a compilation of cases in the pathology literature, there are few clinical series documenting management of these tumours. This paper presents a single-institution analysis of the clinical outcome of patients with intra-abdominal desmoids undergoing surgical exploration with the intent of resection.

The purpose of this report is to assess the outcome of a group of patients with surgically managed intra-abdominal desmoids. Although Burke *et al.*³ reported a compilation of cases in the pathology literature, there are few clinical series documenting management of these tumours. This paper presents a single-institution analysis of the clinical outcome of patients with intra-abdominal desmoids undergoing surgical exploration with the intent of resection.

Patients and methods

Between July 1982 and June 1998 approximately 70 patients with intra-abdominal desmoid tumours were evaluated. Reflecting a conservative surgical approach, 24 patients

came to operation with the intent of resection. This analysis excludes desmoid tumours of the abdominal wall. During this period, 189 patients with extremity and superficial truncal desmoid tumours were operated on^{8,10}.

Patients undergoing operation were followed prospectively. Clinical, operative and pathology reports were reviewed and the histological diagnosis of desmoid tumour was confirmed using standard criteria. Characteristic histological features included bland fibroblastic and myofibroblastic cells arranged in parallel; cells widely separated by abundant collagenous matrix; absence of cellular pleomorphism, mitoses or necrosis; and irregularly spaced, slit-like vessels. Determinations of tumour size and extent of mesenteric involvement by the tumour were made by review of radiology, operative and pathology reports. Follow-up was obtained through the sarcoma database, the surgeons' offices and telephone calls to patients.

Survival was determined by the Kaplan-Meier method and comparison between groups was made with the log rank statistic.

Results

Patients with intra-abdominal and pelvic desmoids comprised 11 per cent of all desmoid tumours treated by surgery at the Memorial Sloan-Kettering Cancer Center. The demographic and clinical features of the 24 patients with intra-abdominal desmoids undergoing operation are outlined in Table 1. For the purpose of this analysis, two groups

of patients were identified: those who had complete resection, defined as complete gross resection of the intra-abdominal desmoid tumour ($n=16$), and those who underwent laparotomy but were deemed irresectable, and had only biopsy either with ($n=4$) or without ($n=4$) intestinal bypass. The symptoms that led to definitive operation in individual patients were characterized as either minor (i.e. asymptomatic, mass or vague abdominal pain) or major (i.e. complications such as obstruction and fistula). Mild symptoms predominated in both groups (Table 1).

During the study period, half of the patients were managed with surgery alone while the others had multimodality treatment which included some combination of sulindac, antioestrogen therapy, cytotoxic chemotherapy and radiotherapy in addition to operation. Interestingly, five patients who had complete resection were managed initially with a combination of biopsy and/or medical therapy before a decision was made to undertake complete resection. Overall, 14 patients had a single operation while ten patients had a total of 27 procedures for the desmoid tumour. Indications for additional operations included initial biopsy before resection ($n=3$), management of postoperative complications ($n=4$), management of complications of disease ($n=6$) and resection of recurrent disease ($n=4$).

The overall survival rate in the 24 patients was 73 per cent at 10 years. Of note, there was no difference in the overall survival rate between the completely resected and unresected groups of patients ($P=0.73$). Eleven of 16

Table 1 Patient and treatment data

	Patients with abdominal desmoid tumour	Resected patients	Unresected patients
No. of patients	24	16	8
Median (range) age (years)	39 (18-73)	32 (18-73)	45 (26-61)
Sex ratio (M:F)	12:12	9:7	3:5
Previous abdominal surgery	10	6	4
Familial adenomatous polyposis	5	2	3
Associated abdominal wall desmoid	5	2	3
Presenting symptoms			
Mild	18	13	5
Major	6	3	3
Treatment modality			
Surgery only	12	10	2
Chemotherapy	2	1	1
Tamoxifen or sulindac	10	5	5
Radiation	6	4	2
Surgical data			
Total laparotomy	41	30	11
Abdominal origin	18	12	6
Pelvic origin	6	4	2
Median (range) tumour size (cm)	14 (4-25)	14 (4-24)	15 (8-25)
Mesenteric involvement	18	12	6

completely resected patients had no evidence of disease at a median follow-up of 62 months. Although most patients undergoing complete resection had positive histological margins, the majority had no recurrence at follow-up. Five of eight patients in the unresected group were alive with disease at a median follow-up of 59.5 months (Table 2). These five patients have had a median follow-up of 86 months.

In this series, all the patients with FAP had undergone a previous total abdominal colectomy and all presented with abdominal wall desmoid disease in addition to the intra-abdominal desmoids. Two patients with FAP underwent complete resection of the intra-abdominal tumour; they later developed recurrence and died from desmoid disease. The three patients with FAP who were unresected are alive with disease at a median follow-up of 36 months.

Among the 24 patients, progressive symptoms mandated reoperation in five individuals who were initially operated on and not resected. Three of these patients' tumours were completely resected at the time of reoperation; one of these patients remains disease free, another had recurrence and is alive with disease more than 9 years after initial operation, while the third died from recurrent disease and short gut after two further operations. The remaining two patients include a patient who had a small intestinal bypass and another who required resection of the small intestine because of fistulas. The former patient had further progression of disease and died, whereas the latter remains well and has no evidence of progression of the unresected intra-abdominal desmoid more than 10 years after the first laparotomy for desmoid disease.

Six of the 16 completely resected patients had subsequent recurrence after a median of 26 months. In four cases, reoperation was undertaken. Three of these patients were

re-resected; two of the three had no evidence of disease at the most recent follow-up, while the other recurred again and died from the disease. The tumour in the fourth patient was found to be irresectable, and the patient later died from the disease. One patient who developed recurrence and did not undergo reoperation is alive with disease at a follow-up of 26 months, whereas the other died from the disease after multiple courses of chemotherapy and radiotherapy.

Significant morbidity and mortality occurred in some patients in whom complete resection was undertaken, usually because of intestinal resection. Three patients had substantial morbidity because of small bowel loss, and two of them have died. Two of the three patients developed small intestinal ischaemia due to a mesenteric vascular catastrophe in the immediate postoperative period and required complete small bowel removal. One of these patients died and the other is maintained on home total parenteral nutrition. A further three patients had extensive small bowel resections but maintain adequate nutrition and weight, although they have frequent bowel movements and require periodic gastroenterological follow-up. Two other patients whose intra-abdominal desmoids had a significant pelvic component incurred morbidity secondary to chronic, severe, lower extremity lymphoedema in one patient and to footdrop in the other.

Involvement of the mesentery appeared to be associated with surgical morbidity and mortality in this series, as the one postoperative death and the cases involving massive intestinal resection all occurred in patients with mesenteric involvement by desmoid tumour. Moreover, all six patients in this series who died as a result of disease or treatment had involvement of the mesentery.

There was a total of seven deaths among the 24 patients. In the unresected group, two of eight patients died from

Table 2 Patient outcome and follow-up

	Patients with abdominal desmoid tumours	Resected patients	Unresected patients
No. of patients	24	16	8
Median (range) length of small intestine resected (cm)	—	49 (10–432)*	—
Microscopic margin†			
Positive	—	11	—
Negative	—	3	—
Follow-up (months)	62.0	62.0	59.5
Disease status			
No evidence of disease	11	11	0
Alive with disease	6	1	5
Died from disease	5	3	2
Died from other causes‡	2	1	1
Actuarial survival rate at 100 months (%)	73	76	67

*Data available for ten of 12 relevant cases; †data available for 14 patients; ‡includes one postoperative death

progression of disease, characterized by small bowel obstruction and sepsis. The third patient died as a result of a rapidly progressive adenocarcinoma, nearly 8 years after he first underwent exploration for an intra-abdominal desmoid. One of the five patients alive with disease in the unresected group has been operated on for complications of disease and two others had documented partial regression of the tumour. Three of the four deaths in the resected group were due to progressive disease resulting in intestinal obstruction, fistula formation and sepsis.

Discussion

Reports on the clinical management of intra-abdominal desmoid tumours generally comprise small numbers of patients and frequently include intra-abdominal desmoids together with abdominal wall and extremity lesions. However, intra-abdominal desmoids warrant separate

attention because their location may predispose to marked morbidity due to disease progression as well as treatment. Unlike extremity desmoids, which rarely, if ever, cause death, intra-abdominal desmoids are associated with a defined mortality rate^{1,3,8,10}. Therapeutic decision-making is challenging because surgical resection of these lesions is technically difficult and accompanied by a significant risk of complication, while medical therapy is of unclear benefit¹¹.

This study indicates that prolonged survival is possible in patients who develop intra-abdominal desmoid tumours, even for those with technically irresectable or recurrent lesions. In fact, some patients may even experience regression of disease (*Figs 1 and 2*). Complications occurred in only a minority of unresected patients and operative intervention after development of complications effectively palliated some patients for long periods. Burke *et al.*³ reported similar findings, as eight of the ten irresectable

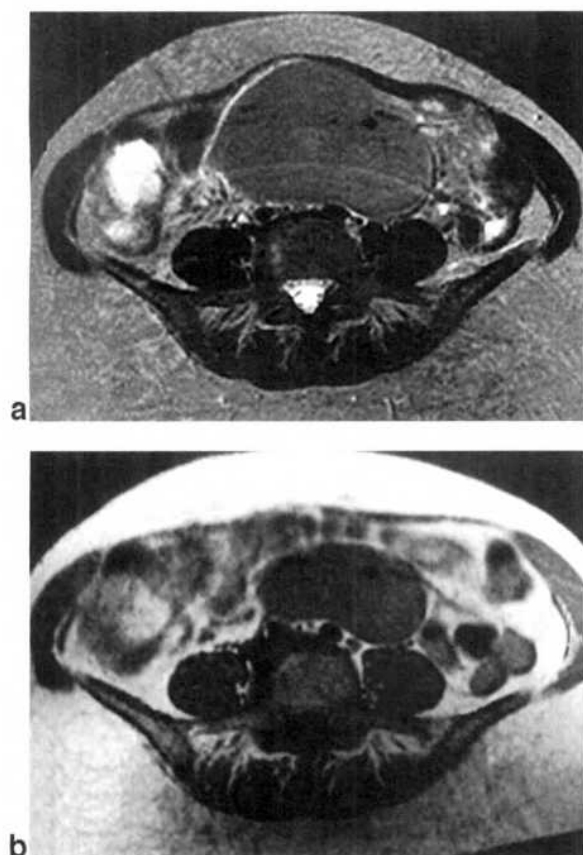


Fig. 1 Cross-sectional magnetic resonance images of a 60-year-old woman with a clinically diagnosed intra-abdominal desmoid tumour. The patient was treated with sulindac only. The tumour regressed from a maximum diameter of **a** 12 cm in August 1997 to **b** 8.5 cm in January 1999. The patient remains asymptomatic

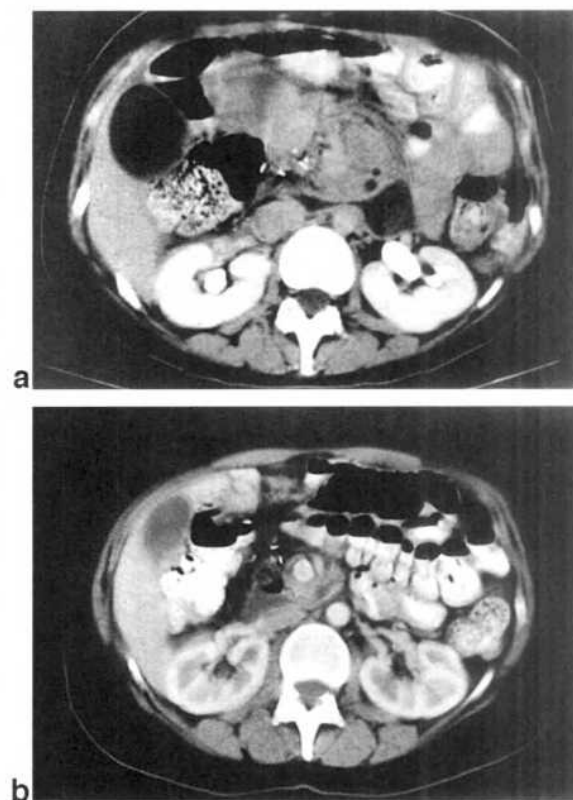


Fig. 2 **a** Cross-sectional computed tomogram of a 51-year-old woman who presented with bowel obstruction due to an intra-abdominal desmoid tumour in 1993. The lesion was irresectable and intestinal bypass was performed.

b Follow-up imaging in 1998 demonstrated substantial regression of the tumour mass. The patient is only mildly symptomatic and has received no treatment

Table 3 Surgical resection of intra-abdominal desmoid tumours reported in the literature

Reference	Year	No. of patients	No. resected	Tumours associated with mesentery	Deaths from surgical complication	Patients with recurrence	Death from disease
Dong-Heup <i>et al.</i> ¹²	1971	9	9	6	2	3	1
Posner <i>et al.</i> ⁸	1989	19	—	—	—	—	5
Burke <i>et al.</i> ³	1990	130	114	74	8 of 70	16 of 70	4 of 70
Bruce <i>et al.</i> ^{1*}	1996	18	18	—	0	2 of 8	0

*Review of sporadic cases; the cases from References 1 and 3 were not included in the summary chart

patients in their series were alive at last follow-up and none had demonstrated tumour enlargement. Therefore, the biology of intra-abdominal desmoids may be characterized by initial rapid growth followed by stability or regression.

Complete resection may be associated with apparent cure in a majority of resected patients, especially those with sporadic desmoid tumours. Of note, resection for cure was not dependent on a negative histological margin, as most completely resected patients with positive margins had no evidence of recurrence after a median follow-up of 4 years. It should be stressed, however, that substantial morbidity can be incurred by attempts at resection. This is usually due to the need for extensive small bowel resection, either to encompass the entire tumour or because of mesenteric vascular compromise. Mesenteric involvement, a common feature of intra-abdominal desmoids, and resultant proximity of the mesenteric vessels to the line of resection, is a critical factor governing this increased attendant morbidity rate. Significant small bowel loss resulted from one-third of the operations in resected patients in the present series. Although not intended as part of the planned procedure, near-total enterectomy was performed in three patients. Other authors have alluded to the potential for morbidity associated with extirpation of these tumours (*Table 3*).

Desmoids are noted for their proclivity to recur following resection in up to one-third of cases. However, recurrent disease can be resected and patients may live for extended periods with recurrent disease, especially in cases of sporadic desmoid tumours. Patients with FAP represent a particularly complex group. These patients usually have associated abdominal wall desmoids and may have particularly aggressive intra-abdominal disease, prone to complications and recurrence^{2,3}. This report lends support to the contention that these patients are best managed without resection for as long as possible¹³.

Recently, small intestinal transplantation has been undertaken for the management of intra-abdominal desmoids¹⁴. Unfortunately, this is still a relatively unproven therapy, and 3-year patient survival rates remain less than 70

per cent. Moreover, patients with FAP, who might require this radical approach the most, are at significant risk for death from colorectal cancer and periampullary cancer – a risk that conceivably would be heightened by the immunosuppression necessary for graft survival¹¹.

In conclusion, the results presented here suggest that resection of intra-abdominal desmoid tumours is frequently curative but may be associated with a high cost in terms of morbidity and mortality. Furthermore, the biology of these tumours is unpredictable and may be a more important determinant of outcome than the treatment rendered¹⁵. Some patients, especially those with FAP, are at high risk of recurrence following tumour excision. None the less, as demonstrated in extremity desmoids, many of these patients may have prolonged survival even if the tumour is recurrent or unresected¹⁶. Heroic resections that endanger the viability of the small intestine and the patient should be avoided if possible. Given that these tumours may be associated with minimal symptomatology, a trial of watchful waiting and minimally toxic medical therapy (e.g. antioestrogens, sulindac) may be preferable to resection, especially in patients with lesions intimately involved with the mesenteric vessels and in those with FAP. If complications do arise, operations to palliate complications such as obstruction should be considered.

Acknowledgements

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Diagnostic failures in endoscopy for acute upper gastrointestinal haemorrhage

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Background: Oesophagogastrroduodenoscopy (OGD) is the diagnostic tool of choice in acute upper gastrointestinal haemorrhage. However, the factors causing diagnostic failure are not well documented or discussed.

Methods: OGDs performed by a single surgeon for acute upper gastrointestinal haemorrhage were reviewed retrospectively for 'missed' diagnosis.

Results: There were nine cases (1.4 per cent) of 'missed' diagnosis in 638 OGDs performed over a 3-year period. Incomplete examination caused by a fundal pool precluded three examinations in which two Dieulafoy's lesions and one chronic gastric ulcer were later found. Other difficult examination sites were the cardia/high lesser curve (three cases), the stomal line of a gastrojejunostomy anastomosis (two) and at the junction of the first and second part of the duodenum (one). Four of the overlooked diagnoses were Dieulafoy's lesions.

Conclusion: OGD was able to diagnose the cause of bleeding in 98.6 per cent of patients with acute upper gastrointestinal haemorrhage. The factors that caused diagnostic failure were a difficult examination site and failure to recognize lesions (Dieulafoy's).

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Introduction

Surgical endoscopy is an essential part of surgical training and should be part of the armamentarium of a general surgeon. The two developments that have advanced this field are the manoeuvrable fibre optic tip and the video charge coupled device chip¹. These have led to greater accuracy of diagnosis in the management of acute upper gastrointestinal haemorrhage and have also allowed subsequent endoscopic therapy. Oesophagogastrroduodenoscopy (OGD) has superseded barium imaging and is the first-line investigation in the management of acute upper gastrointestinal haemorrhage^{2,3}.

However, there are diagnostic problems associated with endoscopy in acute upper gastrointestinal haemorrhage which are not well documented despite their importance, not only to trainees but also to trained endoscopists. Hence, a retrospective review of the endoscopic records of a single operator was undertaken to determine the cause of diagnostic failure in OGD examinations performed for acute upper gastrointestinal haemorrhage.

Patients and methods

The prospective computer database of a single surgeon's endoscopies (Y.F.A.C.) was reviewed. Records of consecutive OGDs performed for acute upper gastrointestinal haemorrhage between 1995 and 1998 were identified. Acute upper gastrointestinal haemorrhage was defined as clinical presentation of haematemesis, melaena or bloody nasogastric aspirate. Patients with anaemia at presentation or a drop in haemoglobin level without clinical evidence of bleeding were excluded from the review.

Initial OGDs that failed to reveal a probable source of haemorrhage in the upper gastrointestinal tract were identified. During the same hospital admission these patients were routinely followed up with subsequent repeat OGD when there was incomplete examination or evidence of a rebleed. The final diagnosis and factors that may have interfered with diagnosis were recorded.

All patients had emergency OGD performed with a forward-viewing panendoscope (GIF-100; Olympus Optical, Tokyo, Japan) linked to the video system (CV-

60; Olympus Optical) and light source (CLV-U20; Olympus Optical). A side-viewing scope (JF-100;

Table 1 Final diagnosis and site of lesions 'missed' by oesophagogastroduodenoscopy for acute upper gastrointestinal haemorrhage

	No.	'Missed'	Site
Gastric ulcer	178 (27.9)	1	Fundal pool
Duodenal ulcer	171 (26.8)	1	D1/D2 junction
Gastritis/erosions	52 (8.2)		
Varices	45 (7.1)		
Neoplasm	34 (5.3)	1	Cardia/high lesser curve
Erosive duodenitis	18 (2.8)		
Oesophagitis	17 (2.7)		
Stomal ulcer	14 (2.2)	2	At/beyond gastrojejunostomy anastomosis
Mallory–Weiss lesion	10 (1.6)		
Dieulafoy's lesion	6 (0.9)	4	2, Fundal pool 2, Cardia/high lesser curve
Other	93 (14.6)		

Olympus Optical) was used on selected patients when necessary. The patients were examined within 24 h of admission in the endoscopy suite under topical analgesia or light sedation. Immediate OGD was performed on patients who experienced ongoing bleeding or haemodynamic instability at presentation after a brief period of resuscitation.

Results

Over a period of 3 years, 1701 consecutive OGDs were performed, of which 638 (37.5 per cent) were for acute upper gastrointestinal haemorrhage. There were nine (1.4 per cent) 'missed' diagnoses that required repeat OGD (Table 1).

Peptic ulceration was the most common cause of acute upper gastrointestinal haemorrhage (56.9 per cent). There were four specific sites in the upper gastrointestinal tract at which bleeding lesions were missed and which required repeat endoscopy (Fig. 1). Three lesions were found beneath the fundal pool while three were located at the

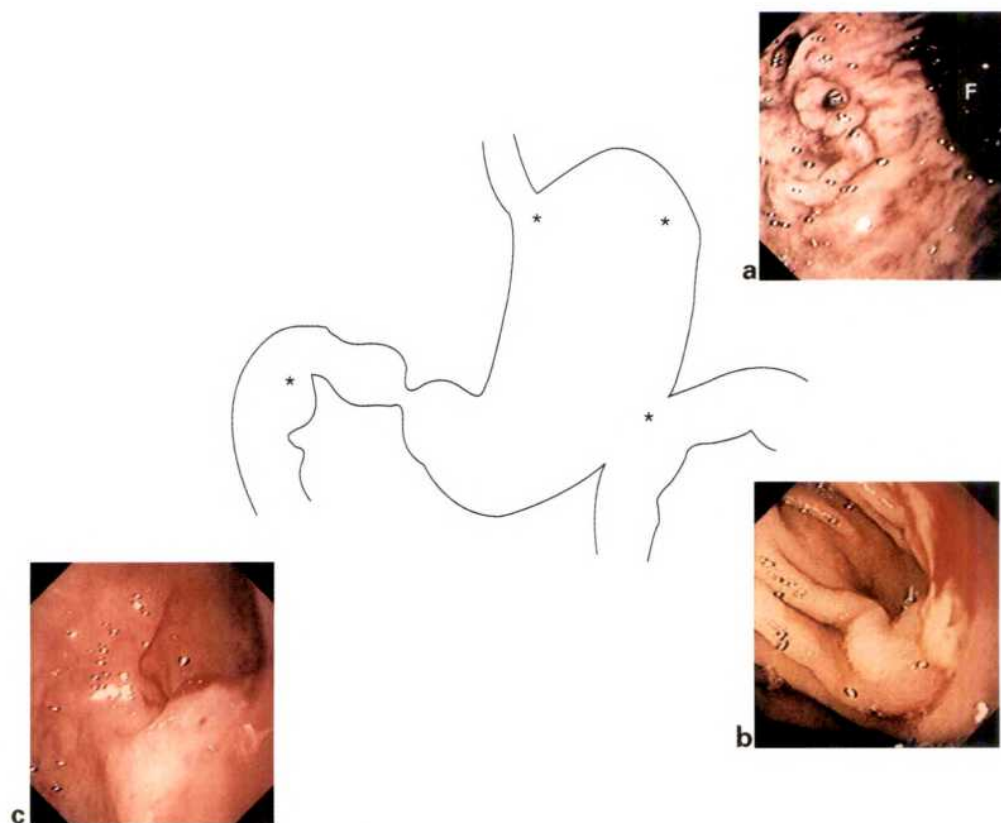


Fig. 1 Sites of 'missed' diagnosis of acute upper gastrointestinal haemorrhage (*).

- a A Dieulafoy's lesion underneath the fundal pool (F) on repeat oesophagogastroduodenoscopy after aggressive nasogastric lavage and right lateral decubitus positioning of the patient.
- b An oozing chronic stomal ulcer at the superior gastrojejunostomy anastomosis.
- c A bleeding chronic duodenal ulcer at the D1/D2 junction examined with a side-viewing scope

cardia/high lesser curve. Two patients with stomal ulcers at or just beyond the gastrojejunostomy anastomosis had previously had a Billroth II type gastric resection. One patient had a chronic duodenal ulcer at the junction of the first and second part of the duodenum (D1/D2). The most commonly overlooked source of bleeding was a Dieulafoy's lesion in the proximal part of the stomach. Four of six patients needed repeat OGD to make the diagnosis.

Ninety-three patients (14.6 per cent) had normal OGD or no diagnosis of upper gastrointestinal haemorrhage. Subsequent investigations and follow-up of these patients revealed the bleeding to be localized to other parts of the gastrointestinal tract. None of these patients had bleeding from the upper gastrointestinal tract within the examination field of the OGD.

Discussion

Using OGD, it was possible to make an accurate diagnosis in 98.6 per cent of patients who presented with acute upper gastrointestinal haemorrhage. Failure of diagnosis was related to two causes, a difficult examination site and failure to recognize rare bleeding lesions.

Excessive blood covering the examination field was a frequent cause of incomplete OGD and was reported to range between 3.8 and 13 per cent in large series⁴⁻⁶. A fundal pool that contains blood or clots in the gastric fundus can preclude complete mucosal visualization, with failure to diagnose the bleeding lesion. Stollman *et al.*⁶ found significantly more causes of bleeding related to portal hypertension in the initial uncleared fundal pool compared with controls. Repeat endoscopy in these patients revealed previously undiagnosed lesions in 41 per cent and they were also predominantly related to portal hypertension. Wu *et al.*⁷ found gastric ulcer to be the main cause in a series of missed lesions but deaths in their series were related to underlying liver disease. The present review included three cases (0.5 per cent) of fundal pool precluding a complete examination. These were found to harbour two Dieulafoy's lesions and one gastric ulcer.

Every effort should be made to clear the fundal pool at the time of examination. Placing the patient in an upright or right lateral decubitus position will help unless the pool is large or adherent. Failing this manoeuvre, gastric lavage with an overtube, large-bore naso/orogastric tube or even *in situ* large-channel therapeutic scopes may reduce the size of the pool to allow adequate examination⁸. Alternatively, repeat OGD should be planned within the next 12–24 h in haemodynamically stable patients.

Peptic ulceration (56.9 per cent) remained the most common cause of acute upper gastrointestinal haemorrhage, a similar finding to that of other large studies^{4,9}. The

diagnosis was usually obvious except at difficult sites where examination was compromised. Following gastric resection there is increased gastric emptying, so any bleeding or clot is rapidly cleared giving a false-negative examination. Thus close surveillance of the gastrojejunal stomal line and just beyond it is imperative in the case of acute upper gastrointestinal haemorrhage. Retroflexion of the endoscope tip to visualize the superior stomal line is necessary although it may be difficult in a small remnant stomach. A side-viewing scope is thus preferable to visualize the entire stomal line. The junction between D1 and D2 was the other site at which a chronic duodenal ulcer was missed. The use of a side-viewing scope will also enable the region to be visualized.

The cardia/high lesser curve region was also a common site at which bleeding lesions were overlooked. The difficulty arises especially when there is inability to distend the stomach fully in an uncooperative patient, thus preventing complete retroflexion of the OGD tip to view the cardia at close range. The presence of a fundal pool may also limit the visualization in this area.

Four of six Dieulafoy's lesions in this series required repeat endoscopy for diagnosis. This lesion is often overlooked and unrecognized rather than rare¹⁰. Endoscopically, it is a small lesion in the form of a protuberant vessel with no mucosal ulceration and is mainly located in the proximal stomach. There are recent reports of endoscopic diagnosis with favourable endoscopic treatment, although repeat endoscopy for diagnosis is still common¹⁰⁻¹². The endoscopist needs a high index of suspicion during a difficult OGD for acute upper gastrointestinal haemorrhage.

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Changing pattern of histological type, location, stage and outcome of surgical treatment of gastric carcinoma

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Background: There are indications that some features of gastric carcinoma are changing, with a possible impact on prognosis. The aim of this study was to examine any changes in type, location, stage, resection rate, postoperative mortality rate or prognosis for patients with gastric carcinoma in a well defined population.

Methods: During 1974–1991, 1161 new cases of gastric adenocarcinoma were diagnosed in Östergötland County, Sweden. Tumour location, Laurén histological type, tumour node metastasis (TNM) stage, radicality of tumour resection and postoperative complications were recorded after histological re-evaluation of tissue specimens and examination of all patient records. Dates of death were obtained from the Swedish Central Bureau of Statistics. Time trends were studied by comparing the intervals 1974–1982 (period 1) and 1983–1991 (period 2).

Results: The proportion of diffuse type of adenocarcinoma increased (from 27 to 35 per cent), while that of mixed type decreased (from 16 to 9 per cent) and that of intestinal type was unchanged. The proportion of tumours located in the proximal two-thirds of the stomach increased (from 32 to 42 per cent) and the proportion of patients with tumours in TNM stage IV decreased (from 32 to 25 per cent). Overall tumour resection rates were unchanged, although the proportion of radical total gastrectomies increased (from 36 to 50 per cent). Excluding tumours of the cardia or gastric remnant after previous ulcer surgery, the 5-year relative survival rate after radical resection increased from 25 to 36 per cent and the postoperative mortality rate decreased for both radical (from 11 to 4 per cent) and palliative (from 18 to 6 per cent) resection.

Conclusion: The patterns of tumour histology, location and stage of gastric carcinoma have changed in the authors' region. These changes were paralleled by a significant improvement in survival and postoperative mortality rates.

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Introduction

Although incidence rates decreased during the second half of the twentieth century, adenocarcinoma of the stomach still contributes substantially to cancer deaths in the Western world^{1–4}. Factors that have an effect on survival time are tumour stage, type and location, which are reflected in the rates and radicality of surgical resection^{2,5–12}. For patients undergoing tumour resection, the prognosis is also influenced by the postoperative mortality rate.

Globally, the incidence:mortality ratios for gastric cancer have increased¹. On a local level, some recent studies have shown improved long-term survival rates after surgical treatment^{6,13,14}, while other somewhat earlier studies showed no improvement^{15,16}. The differences between

the studies may be related to differences regarding type, location, stage and resection rates of gastric cancer. When histologically classified according to Laurén¹⁷, the incidence of the intestinal type of gastric cancer seems to have decreased more than that of the diffuse type^{1,5,18,19}, although not all authors have found this trend²⁰. A shift in the location of gastric cancer from the distal to the proximal part of the stomach has been reported consistently^{2,5,6,16,21–24}. Some authors have found an increase in the proportion of early or stage I–II gastric cancer^{5,13,14,25,26}, whereas others have not^{16,27,28}. Resection rates have been reported to increase and postoperative mortality rates to decrease^{6,7,13,14}.

The aim of the present population-based study was to examine whether there have been changes regarding

histological type, location, stage, resection rate and post-operative mortality rate with effects on the survival of patients with gastric cancer.

Patients and methods

Östergötland County is located in south-east Sweden. There are three main hospitals (Linköping, Norrköping and Motala) with well defined local catchment areas (total population approximately 390 000). The University Hospital of Linköping is a regional hospital for a larger area of south-east Sweden, which has its own regional tumour registry. Clinical (date, place, means of diagnosis and tumour location) and histopathological data for all patients with newly detected malignant gastric neoplasia during the 18-year period 1974–1991 in the local catchment areas of the three hospitals were extracted from this registry. Data for patients registered as having adenocarcinoma of the distal oesophagus were also extracted and cross-checked with those for patients with gastric cancer. A total of 1483 malignant tumours of the stomach had been reported to the registry. Of these, 105 were diagnosed by radiological examination only and 47 were not malignant neoplasias (adenoma or dysplasia) or were wrongly registered neoplasias of organs other than the stomach, as shown by histological re-evaluation or examination of patient records. Of the remaining 1331 patients, 1282 had adenocarcinoma and 49 had other malignant tumours of the stomach (21 lymphomas, 18 leiomyosarcomas, seven carcinoids, two squamous cell carcinomas and one histiocytoma). Of the adenocarcinomas, 121 were diagnosed primarily at autopsy. After excluding the latter, the study included 1161 patients with a diagnosis of histologically verified gastric adenocarcinoma while alive.

Histological re-evaluation of sections (old and newly prepared from preserved paraffin blocks) from biopsies, resected specimens or autopsy samples was possible in 1120 cases. For the remaining 41 cases, tissue samples were not retrievable and evaluation was based on histopathological findings and autopsy reports. These were also scrutinized in all other cases, as were the patient records in the three hospitals. The latter included the occurrence and outcome (including death) of postoperative complications during the hospital stay or before the first postoperative outpatient visit after operation (usually within 1–2 months after discharge). As there was no ongoing systematic search for minor complications (e.g. uncomplicated wound infection, urinary infection, superficial venous thrombosis), only major complications have been included.

After examining the surgeon's reports, autopsy reports, histopathology reports and re-evaluation of the tissue specimens, 848 tumours could be staged according to the

tumour node metastasis (TNM) system²⁹. The depth of tumour invasion could be evaluated in 916 cases and classification according to Laurén¹⁷ was possible in 1089 cases. The absence or presence of residual tumour after surgical treatment was classified as R₀ (no residual tumour), R₁ (microscopic residual tumour) or R₂ (macroscopic residual tumour)²⁹. In this paper, 'radical resection' is considered equivalent to R₀ and 'palliative resection' equivalent to R₁ or R₂ resection.

Statistical analysis

Time trends were studied by comparing the two 9-year periods 1974–1982 (period 1) and 1983–1991 (period 2). The main reason for choosing only two time periods was so that the number of cases in each subgroup in each period would be large enough to draw conclusions. For nominal data, the null hypothesis was tested with the χ^2 test or Fisher's exact test, as appropriate. Proportions are given with 95 per cent confidence intervals (c.i.) when relevant. Continuous data were evaluated with the Student *t* test.

Life expectancy in months (from the date of diagnosis) for all ages of each sex and survival data (date and cause of death) were extracted from the files of the Swedish Central Bureau of Statistics, the latest survey being performed in July 1998. Survival data were available for all 1161 patients. Relative survival was then calculated for each patient as: observed survival $\times$ 100/expected survival. Kaplan–Meier analysis was used to calculate cumulative relative survival rates, which are given with 95 per cent c.i. Differences in survival rates between groups were analysed with log rank test. Cox's proportional hazards model was used to determine the prognostic value of tumour location, microscopic type, TNM stage and time of diagnosis. For all tests, a two-tailed *P* value of less than 0.05 was considered to be significant.

Results

The mean age-adjusted annual incidence of adenocarcinoma of the stomach in the county decreased from 30.1 per 100 000 in period 1 to 20.0 per 100 000 in period 2 for men, and from 13.9 per 100 000 in period 1 to 11.2 per 100 000 in period 2 for women. The proportion of women increased from 203 (36 (95 per cent c.i. 32–40) per cent) of 570 in period 1 to 249 (42 (38–46) per cent) of 591 in period 2 (*P* < 0.03). The median (range) age in men was 71 (21–91) years in period 1 and 72 (33–95) years in period 2 (*P* < 0.04). Corresponding values for women were 72 (27–91) and 74 (33–96) years respectively (*P* < 0.03).

Table 1 Tumour location in 1161 patients with gastric adenocarcinoma in the time period 1974–1982 (period 1) and 1983–1991 (period 2)

Location	Period 1	Period 2	Total
Cardia	61 (11)	68 (12)	129 (11)
Body	124 (22)	178 (30)	302 (26)
Antrum	133 (23)	140 (24)	273 (24)
Body and antrum	119 (21)	76 (13)	195 (17)
Gastric remnant	51 (9)	54 (9)	105 (9)
Undefined	82 (14)	75 (13)	157 (14)
Total	570 (100)	591 (100)	1161 (100)

Values in parentheses are percentages. $P < 0.002$ (two-tailed χ^2 test)

Tumour location

As shown in *Table 1*, the proportion of tumours in the cardia did not change significantly, whereas the proportion localized in the gastric body increased ($P < 0.002$) and the proportion localized in both the body and antrum decreased ($P < 0.001$). The proportion of tumours in the proximal two-thirds of the stomach, including the cardia, increased from 185 (32 (95 per cent c.i. 29–37) per cent) of 570 patients to 246 (42 (38–46) per cent) of 591 ($P < 0.002$). Considering patients undergoing radical (R_0) resection (whole study period), the 5-year relative survival rate was 20 (7–33) per cent for patients with tumour in the cardia, 35 (27–44) per cent for those with tumour in the body, 31 (24–39) per cent for those with tumour in the antrum and 19 (8–30) per cent for those with tumour in both body and antrum (cardia *versus* other locations, $P < 0.002$). For patients with tumour in the gastric remnant after previous ulcer surgery, the corresponding 5-year survival rate was 29 (15–44) per cent.

Histological type

Table 2 shows the distribution according to Laurén's histological classification in periods 1 and 2. There was an increase in the proportion of diffuse type ($P < 0.003$), a decrease in the proportion of mixed type ($P < 0.001$) and an unchanged proportion of intestinal type. Regarding patients having radical resection (whole study period), the 5-year survival rate was 34 (27–41) per cent for intestinal, 30 (21–38) per cent for diffuse and 13 (6–21) per cent for the mixed type of adenocarcinoma (intestinal or diffuse *versus* mixed type, $P < 0.001$). There were no significant differences in survival rates after radical resection related to histological type for TNM stages I or II. Considering stage III, the 5-year survival rate was better for intestinal (13 (5–21) per cent) than for diffuse (7 (0–15) per cent) and mixed type (6 (0–13) per cent) ($P < 0.05$ and $P < 0.04$ respectively).

Table 2 Histological type according to Laurén in 1161 patients with gastric adenocarcinoma in the time periods 1974–1982 (period 1) and 1983–1991 (period 2)

Laurén classification	Period 1	Period 2	Total
Intestinal type	270 (47)	298 (50)	568 (49)
Diffuse type	152 (27)	208 (35)	360 (31)
Mixed type	94 (16)	56 (9)	150 (13)
Other or undefined	54 (9)	29 (5)	83 (7)
Total	570 (100)	591 (100)	1161 (100)

Values in parentheses are percentages. $P < 0.001$ (two-tailed χ^2 test)

Table 3 Tumour node metastasis stage in 1161 patients with gastric adenocarcinoma in the time periods 1974–1982 (period 1) and 1983–1991 (period 2)

TNM stage	Period 1	Period 2	Total
IA	18 (3)	27 (5)	45 (4)
IB	77 (14)	63 (11)	140 (12)
II	49 (9)	49 (8)	98 (8)
IIIA	63 (11)	55 (9)	118 (10)
IIIB	52 (9)	66 (11)	118 (10)
IV	180 (32)	149 (25)	329 (28)
Undefined	131 (23)	182 (31)	313 (27)
Total	570 (100)	591 (100)	1161 (100)

Values in parentheses are percentages. TNM, tumour node metastasis. $P < 0.02$ (two-tailed χ^2 test)

Stage

Early gastric cancer was diagnosed in 21 (4 (3–7) per cent) of 481 patients in period 1 and in 30 (7 (5–10) per cent) of 435 in period 2 (P not significant). TNM stages are given in *Table 3*, which shows that, overall, there was a decrease in stage IV tumours from 180 (32 (28–36) per cent) of 570 in period 1 to 149 (25 (22–29) per cent) of 591 in period 2 ($P < 0.02$), but otherwise no systematic changes. Of patients with tumour in the cardia, 20 (33 (21–46) per cent) of 61 in period 1 and 14 (21 (12–32) per cent) of 68 in period 2 had stage IV disease (P not significant). With regard to patients having radical resection (whole study period), the prevalence of stage I disease was eight (24 (11–42) per cent) of 33 for tumours in the cardia, 46 (41 (32–50) per cent) of 113 for tumours in the body, 56 (42 (33–51) per cent) of 134 for tumours in the antrum, nine (18 (8–31) per cent) of 51 for tumours in both the body and antrum, and 25 (64 (47–79) per cent) of 39 for tumours in the gastric remnant after previous ulcer surgery ($P < 0.001$). Following radical resection (whole study period), the 5-year survival rate was 49 (41–57) per cent for stage I tumours, 16 (8–25) per cent for

Table 4 Type and frequency of major postoperative complications among patients treated with radical (R₀) and palliative (R₁ or R₂) resection of gastric adenocarcinoma during the time periods 1974–1982 (period 1) and 1983–1991 (period 2)

Complication	Radical resection				Palliative resection			
	Postop. complications		Postop. deaths		Postop. complications		Postop. deaths	
	Period 1 (n=184)	Period 2 (n=221)	Period 1 (n=184)	Period 2 (n=221)	Period 1 (n=97)	Period 2 (n=80)	Period 1 (n=97)	Period 2 (n=80)
Intra-abdominal bleeding	7 (4)	3 (1)	1 (1)	0 (0)	3 (3)	3 (4)	2 (2)	0 (0)
Anastomotic leakage	19 (10)	7 (3)†	9 (5)	3 (1)‡	9 (9)	7 (9)	6 (6)	2 (2)
Intra-abdominal abscess or peritonitis	2 (1)	1 (0)	1 (1)	0 (0)	4 (4)	2 (2)	1 (1)	0 (0)
Mechanical ileus, including anastomotic stricture	4 (2)	4 (2)	1 (1)	0 (0)	4 (4)	2 (2)	1 (1)	0 (0)
Pneumonia or pulmonary empyema	11 (6)	6 (3)	2 (1)	0 (0)	6 (6)	1 (1)	2 (2)	0 (0)
Pulmonary embolism	2 (1)	2 (1)	1 (1)	1 (0)	1 (1)	1 (1)	0 (0)	1 (1)
Myocardial infarction	2 (1)	3 (1)	2 (1)	1 (0)	2 (2)	1 (1)	1 (1)	1 (1)
Cardiac dysrhythmia or decompensation	3 (2)	3 (1)	1 (1)	1 (0)	1 (1)	0 (0)	1 (1)	0 (0)
Other	11 (6)	10 (5)	2 (1)	2 (1)	7 (7)	4 (5)	3 (3)	1 (1)
Total	61 (33)	39 (18)*	20 (11)	8 (4)†	37 (38)	21 (26)	17 (18)	5 (6)‡

Values in parentheses are percentages. * $P < 0.001$, † $P < 0.01$, ‡ $P < 0.05$ (period 1 *versus* period 2, two-tailed χ^2 test)

stage II tumours and 10 (5–14) per cent for stage III tumours (stage I *versus* stage II or III, $P < 0.001$). The corresponding 10-year survival rates were 29 (21–38), 14 (6–23) and 3 (0–7) per cent.

Surgical treatment and complications

Of all 1161 patients, 513 (90 per cent) of 570 in period 1 and 536 (91 per cent) of 591 in period 2 were treated in a surgical department. A surgical procedure (exploratory laparotomy with or without non-resectional palliative measures, palliative resection or radical resection) was performed in 426 (75 per cent) of 570 patients in period 1 and in 420 (71 per cent) of 591 in period 2. Palliative (R₁ or R₂) tumour resection was performed in 97 (17 per cent) of 570 in period 1 and in 80 (14 per cent) of 591 in period 2. The corresponding values for radical resection were 184 (32 per cent) of 570 and 221 (37 per cent) of 591. Of patients having radical resection, 67 (36 (95 per cent c.i. 29–44) per cent) of 184 in period 1 and 111 (50 (43–57) per cent) of 221 in period 2 underwent total gastrectomy, whereas partial gastric resection was performed in 114 (62 (55–69) per cent) and 107 (48 (42–55) per cent), and local excision or endoscopic extirpation in three (2 (0–5) per cent) and three (1 (0–4) per cent) respectively ($P < 0.01$). Among all 405 patients undergoing radical resection, 141 had splenectomy (110 of 178 at total gastrectomy and 31 of 227 at partial resection or local excision), 12 had distal pancreatic resection, 11 resection of the colon, and 12 resection of other organs. The rates of

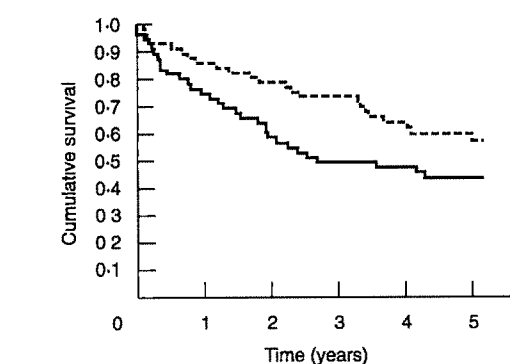
resection of organs other than the stomach did not differ between periods 1 and 2.

Considering patients treated with radical resection in period 1, 37 (44 (33–55) per cent) of 84 with intestinal, 13 (30 (17–45) per cent) of 44 with diffuse, and 15 (35 (21–51) per cent) of 43 with a mixed type of adenocarcinoma had stage I tumours (P not significant). Corresponding values for period 2 were 53 (53 (43–63) per cent) of 100, 19 (32 (21–46) per cent) of 59, and four (13 (4–31) per cent) of 30 (intestinal *versus* diffuse type, $P < 0.02$).

The median age of patients who underwent radical resection was 71 (23–87) years in period 1 and 72 (39–94) years in period 2 ($P < 0.04$). The corresponding values for patients who had palliative resection were 68 (27–84) and 70 (33–87) years respectively (P not significant). There were no differences in resection rates between the two time periods within any of the age groups (20–39, 40–59, 60–79 and 80–99 years).

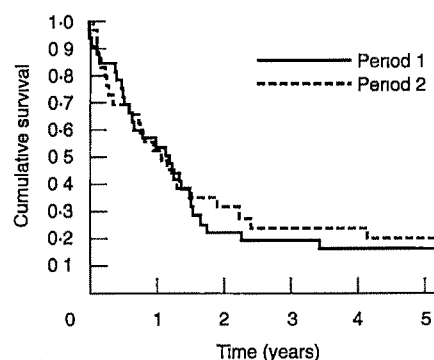
The overall 1-year survival rate was 7 (5–10) per cent for patients having no resection or non-resectional palliative surgery, 12 (8–17) per cent for those who had palliative resection, and 59 (54–64) per cent for patients having radical resection (no resection *versus* palliative resection, and palliative *versus* radical resection, $P < 0.001$). The corresponding 2-year survival rates were 4 (2–6), 3 (0–5) and 41 (36–46) per cent.

Postoperative morbidity and mortality rates are given in Table 4, which shows that both were significantly lower after radical resection in period 2 than in period 1. This



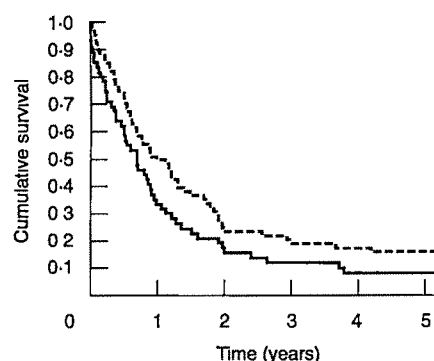
No. at risk

Period 1	55	41	32	27	25	21
Period 2	56	48	44	40	31	23

a TNM stage I ($P < 0.02$)

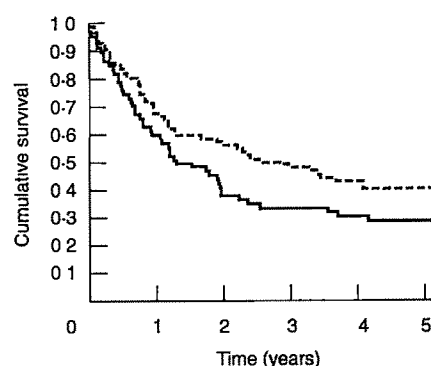
No. at risk

Period 1	32	17	7	6	5	5
Period 2	29	15	9	6	6	3

b TNM stage II (P not significant)

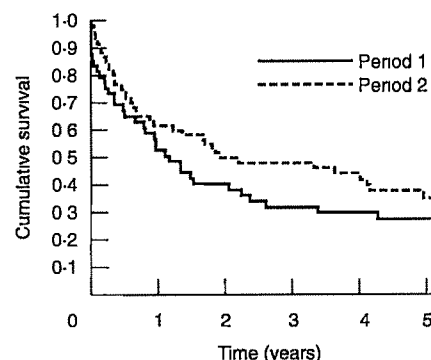
No. at risk

Period 1	55	18	8	6	4	4
Period 2	67	33	15	13	11	10

c TNM stage III ($P < 0.05$)

No. at risk

Period 1	67	40	25	22	20	17
Period 2	86	58	48	40	33	29

a Intestinal type ($P < 0.07$)

No. at risk

Period 1	48	25	19	15	14	13
Period 2	59	36	28	26	22	13

b Diffuse type (P not significant)

Fig. 3 Relative survival for patients treated with radical (R_0) resection of adenocarcinoma of the stomach (excluding patients with tumour in the cardia or gastric remnant after previous ulcer surgery) during period 1 (1974–1982) and period 2 (1983–1991). Log rank test

found in the present study, is that proximal tumours tend to be more advanced when operated on^{5,8}.

Regarding the histological type, there has been a global trend toward a decrease in the incidence of intestinal type, leading to an increase in the proportion of diffuse type of gastric cancer^{1,11,18,19}. This trend is most obvious in high-risk areas where the incidence of the intestinal type is greatest^{1,19,30}. The present study showed an increase in the proportion of diffuse type and a decrease in the proportion of mixed type, while the proportion of intestinal type was unchanged. These results are consistent with those from another part of Sweden²⁰ concerning the time period 1951–1981, although in that study the proportion of diffuse type was unchanged. Nevertheless, it does not seem that the overall fall in the incidence of gastric cancer in Sweden

Fig. 2 Relative survival for patients treated with radical (R_0) resection of adenocarcinoma of the stomach (excluding patients with tumour in the cardia or gastric remnant after previous ulcer surgery) during period 1 (1974–1982) and period 2 (1983–1991). Log rank test

during recent decades is due to a selective decrease in the incidence of the intestinal type of adenocarcinoma.

Overall, there was a tendency (significant for stage III) towards a better survival rate after radical resection for intestinal than for diffuse type of gastric cancer. This is consistent with the fact that, among patients having radical resection, stage I disease was more prevalent in those with intestinal rather than a diffuse type of gastric cancer. When comparing stage for stage within each of the two time periods, there was no difference in survival rate after radical resection between intestinal and diffuse type of gastric cancer. Previous reports concerning survival related to Laurén's classification are conflicting, some showing no difference^{5,9,10,12} and others showing a difference in favour of intestinal type^{2,11,17,30}, or even in favour of the diffuse type³¹. Obviously, the matter is controversial and differences between studies most probably relate to differences in histological interpretation and whether or not proper staging was done.

Although there seemed to be a slight increase in the proportion of early gastric cancer over time, this was not significant. Others have reported similar results^{27,28}, but there are a number of reports showing an increase in the proportion of early gastric cancer during recent decades^{5,13,25,26}. With regard to TNM stage, the present study showed a significant decrease in the incidence of stage IV disease, but otherwise no significant changes, such as increases in the proportion of stage I disease shown by others^{13,14}. As expected^{6,9,10,13,16}, there was an inverse relationship between TNM stage and 5-year survival rate after radical resection. These values are similar to those of others^{6,16}, although considerably higher survival rates have also been reported^{9,10,13}.

Neither the proportion of patients treated in a surgical department nor the overall resection rate differed between the two time periods, although there was a significant increase in the proportion of radical total gastrectomies in period 2. The present resection rates were somewhat lower than those of others^{6,13} who have also reported an increase in the rate of radical resection over time. A review of the literature from 1965 to 1989 indicated that resection rates have tended to increase worldwide¹³. Even though, in general, more patients are undergoing resection, postoperative morbidity and mortality rates have decreased significantly during recent decades^{6,7,13,14}. The present study showed similar results despite the fact that patients undergoing resection were significantly older in period 2 than in period 1.

The rate of postoperative complications after radical resection fell from 33 per cent in period 1 to 18 per cent in period 2, and the postoperative mortality rate fell from 11 to 4 per cent. Two extensive reviews of the literature^{6,7} have

indicated that this decrease in postoperative mortality rate seems to be a trend worldwide. The postoperative mortality rate after palliative resection also decreased from 18 to 6 per cent. The present postoperative complication rates were within the range of those published by others^{10,13,16,27,32,33}. In one of these studies¹³, postoperative morbidity decreased significantly during 1970–1989. Considering the postoperative mortality rate after resection, the latter study showed a decrease from 9 to 5 per cent, and another study, which compared 1975 with 1989, showed a decrease from 13 to 2 per cent⁷. In neither the present nor the studies referred to have changes in postoperative complication rates been studied in relation to possible changes in surgical technique and nutritional status of the patients. Accordingly, it can only be speculated that improvements regarding these factors may explain the decrease in postoperative morbidity rate, especially anastomotic leakage, observed in the present study.

The overall survival rate improved significantly from period 1 to period 2. In a study from Sweden¹⁵ concerning the time period 1960–1978 and another study from USA¹⁶ (North Carolina) concerning 1953–1983, there was no change in overall survival rate. However, several other studies have shown that some improvement has occurred over time, both globally¹ and locally^{6,13,14}. These improvements may be related to changes in awareness of the disease and less delay in diagnosis, diagnostic and surgical strategies, complication rates and altered tumour behaviour. Changes regarding several of these parameters may explain why time was an independent predictor of outcome in the multivariate analysis. Another possible explanation is case selection in some of the reported series. This was, however, not the case in the present study, which included all cases of gastric cancer in a well defined population. Although there was a modest improvement for patients having palliative resection, the improvement in overall survival rate was due mainly to an increase in survival rate among patients having radical resection for stage I tumours and among those having radical resection for the intestinal type of adenocarcinoma of the gastric body, antrum, or both, but not tumours of the cardia or gastric remnant.

In conclusion, this study showed that the proportion of the intestinal type of adenocarcinoma was unchanged, while that of the diffuse type increased and that of mixed type decreased. Furthermore, the proportion of tumours located in the proximal two-thirds of the stomach increased and the proportion of patients with tumours in TNM stage IV decreased. Survival rate improved significantly for patients who had radical tumour resection (excluding tumours of the cardia and gastric remnant after previous ulcer surgery) and there was a significant decrease in postoperative mortality

rate after both radical and palliative tumour resection. These improvements occurred in spite of an increase in median age at diagnosis. Although not specifically investigated or answered by the present study, it may be speculated that a better general condition of patients and improved surgical technique and perioperative care are factors that have contributed to an increase in survival rate after radical resection. These factors, in addition to the postoperative morbidity rate, which dropped significantly, may have effects on the occurrence of late complications and tumour recurrence.

Acknowledgements

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Corrigendum

P. R. O'Connell. What should surgeons write? *Br J Surg* 2000; **87**: 132–4.

Please note that the fourth sentence of the second last paragraph of this article should read as follows: 'Some such texts are excellent examples of the various styles of surgical writing; Bailey and Love's *Short Textbook of Surgery*, Goligher's *Surgery of the Anus, Colon and Rectum*, Sabiston's *Textbook of Surgery* and Schwartz's *Principles of Surgery* are a few personal favourites'.

Surgical Research Society

The following abstracts were presented to the 90th meeting of the Surgical Research Society. The meeting was organized by and held at the Royal Free Hospital in London on 2–3 December 1999. One hundred and twenty-four abstracts were presented

Mutations in the *PRSS1* gene and *CFTR* gene in patients with chronic idiopathic pancreatitis

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Background: In up to 30 per cent of patients with chronic pancreatitis no underlying cause is found despite intensive investigation. Mutations in the cationic trypsinogen gene (*PRSS1*) have been shown to cause hereditary pancreatitis, which has clinical features identical to those of other forms of chronic pancreatitis. Recent studies have also suggested that heterozygous mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene are associated with idiopathic chronic pancreatitis. This study investigated the frequency of mutations of these two genes in patients referred with a presumed diagnosis of idiopathic chronic pancreatitis.

Methods: Forty-eight consecutive patients attending a pancreatic clinic with a diagnosis of idiopathic chronic pancreatitis were studied. Patients ($n=4$) referred with a presumed diagnosis of hereditary pancreatitis were excluded. Venous blood was taken to identify the two known mutations in *PRSS1* and to screen for the 16 most common mutations in *CFTR* (accounting for 85 per cent of cystic fibrosis alleles).

Results: Mutations in *PRSS1*, consistent with a diagnosis of hereditary pancreatitis, were found in nine (19 per cent) of 48 patients with idiopathic chronic pancreatitis. A further nine (25 per cent) of 36 were shown to be heterozygous for *CFTR* mutations, compared with a frequency of 4.8 per cent in 165 control patients ($P=0.003$).

Conclusion: Genetic abnormalities are common in patients with idiopathic chronic pancreatitis. Forty-four per cent of patients seen over a 14-month period either carried a disease-causing mutation in *PRSS1* or were heterozygous for *CFTR* mutations. It is important to consider the possibility of mutations in *PRSS1* or *CFTR* in patients who present with idiopathic chronic pancreatitis.

CD8+ T cells are essential for survival after injury

M. R. Kell, C. Magee, J. A. Mannick and J. A. Lederer (introduced by H. P. Redmond)

during the scientific sessions. The Patey prize was awarded to Mr K. C. Chan for a paper entitled 'Epidermal growth factor receptor inhibition decreases epithelial proliferation in ductal carcinoma *in situ* of the breast, whereas *c-erbB2* blocking does not'.

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Background: It has recently been demonstrated that injury causes an early enhanced T-cell response to bacterial superantigen. This study examined CD4+ and CD8+ T-cell function following burn injury and used genetically engineered CD4+ and CD8+ T cell-deficient mice to investigate the *in vivo* function of these cells after burn injury.

Methods: Wild-type C57B/1-6 (WT) mice were anaesthetized and exposed to sham or 25 per cent scald burn injury. Three cell populations were obtained from splenocytes harvested 2 h after injury: (1) all cells, (2) CD4+ T cell-enriched and (3) CD8+ T cell-enriched groups using negative selection with antibody-coated beads. All three groups were then stimulated with superantigen (staphylococcal enterotoxin B) and cytokine enzyme-linked immunosorbent assays were performed on 48-h supernatants. Next, CD4 and CD8 knockout mice (CD4^{-/-} and CD8^{-/-}) on a C57B/L6 background and WT mice were sham or burn injured and deaths were observed. Finally, CD8-enriched T cells from WT mice were adoptively transferred into CD8^{-/-} mice. Reconstituted mice were then burn injured and 48-h mortality was assessed.

Results: After burn injury there was a switch in the dominant T-cell type producing interferon γ and tumour necrosis factor α from CD4 to CD8 ($P<0.01$). There was a significantly higher mortality rate following injury in CD8^{-/-} mice (12 of 12 animals) compared with WT mice (one of 12) and CD4^{-/-} mice (one of 12) ($P<0.01$). Adoptive transfer of CD8+ T cells into CD8^{-/-} mice improved survival following burn injury (nine of 12; $P<0.01$).

Conclusion: These findings indicate that CD8+ T cells are more important than previously thought following injury. Not only is CD8+ T-cell function unregulated early after injury but CD8+ T cells also appear to be essential for survival following injury.

Effects of chronic aspirin therapy on haemostatic function persist for 5 days after treatment cessation

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Background: Aspirin has a significant effect on haemostasis by prolonging the bleeding time and is associated with increased intraoperative and postoperative bleeding. Patients on long-term aspirin therapy are often advised to discontinue treatment for a period of time before elective surgical procedures, to allow their clotting mechanisms to return to normal. The optimum period of time without taking aspirin has never been determined in a clinical setting. The only guidelines are based on theoretical considerations, but when not taking aspirin these patients may be at risk of thrombosis. The aim of this prospective study was to establish the duration of the aspirin effect on haemostasis following cessation of treatment.

Methods: Forty-five healthy volunteers (mean age 23.5 years, 23 men) were randomly divided, in a double-blinded fashion, into three separate groups. All were screened for any contraindications to aspirin therapy. Subjects in group 1 ($n=15$) received 75 mg aspirin once a day, those in group 2 ($n=15$) received 300 mg aspirin once a day, and those in group 3 ($n=15$) received a placebo. All tablets were identical in appearance. Baseline platelet count, template bleeding time and platelet aggregation test (the platelet function analyser 100) were measured in all subjects (bleeding times provide a measure of the individual's primary haemostatic mechanisms, while aggregation tests specifically reflect platelet function). Following a 14-day course of tablets, the tests were repeated on a daily basis until a return to baseline for 2 consecutive days demonstrated recovery of the individual's haemostatic mechanisms.

Results: Thirty-five volunteers completed the study (12 in group 1, 13 in group 2 and ten in group 3). All bleeding times of volunteers on aspirin had returned to baseline by 96 h, whereas the aggregation tests took 148 h to normalize. There was no detectable haemostatic effect of aspirin in any of the volunteers by the sixth day after stopping treatment. There was no significant difference in duration of effect between the two doses of aspirin. There were two false-positive bleeding time tests and one false-negative aggregation test.

Conclusion: This study demonstrates that the duration of increased bleeding tendency after withdrawal of aspirin therapy is 5 days and establishes practical guidelines governing preoperative aspirin cessation. Clinicians can minimize the preoperative period of time that aspirin is withheld without increasing the risk of excessive bleeding in surgery.

Epidermal growth factor receptor inhibition decreases epithelial proliferation in ductal carcinoma *in situ* of the breast, whereas *c-erbB2* blocking does not

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Background: Ductal carcinoma *in situ* (DCIS) expresses *c-erbB2* and epidermal growth factor receptors. This study aimed to determine whether blocking of either the *c-erbB2* receptor with a monoclonal antibody (Herceptin) or the epidermal growth factor receptor (EGFR) with an EGFR tyrosine kinase inhibitor (ZD 1839) prevented heterodimerization of these two receptors and subsequent signal transduction leading to decreased epithelial proliferation in DCIS.

Methods: DCIS tissue from 18 women undergoing surgery was implanted into 16–20 athymic nude mice per experiment (eight xenografts per mouse). Treatment commenced 2 weeks after implantation and consisted of either five courses of Herceptin (150 g intraperitoneally per course) or daily gavage with ZD 1839 at 75–200 mg kg⁻¹ for 14 days. Appropriate controls were used. Xenografts were removed on days 14, 21 and 28. Epithelial proliferation was assessed by counting 1000 epithelial cells after Ki67 immunostaining.

Results: ZD 1839 inhibited proliferation compared with that in controls after 14 days ($P < 0.005$), whereas Herceptin did not (see Table below).

Conclusion: Proliferation in DCIS is decreased by EGFR tyrosine kinase inhibition but not by *c-erbB2* receptor blocking. EGFR tyrosine kinase inhibitors have potential as adjuvant therapy in DCIS.

Cryopreservation eradicates Gal1-3Gal and Thomsen-Friedenreich expression on porcine pancreatic islets

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Background: The objective of this study was to define the effects of collagenase digestion and cryopreservation on the

Ki67 labelling Index (%)	Day 0	Day 14	Day 28	
			Control	Treatment
<i>c-erbB2</i> group ($n=9$)	16.8 (11.7–23.4)	8.4 (4.2–12.2)	16.2 (9.0–26.3)	19.1 (6.6–19.1)
EGFR group ($n=9$)	19.9 (5.7–30.9)	16.5 (9.8–23.6)	23.0 (2.2–39.2)	3.2* (0–8.3)

Values are median (interquartile range) EGFR, epidermal growth factor receptor. * $P < 0.005$ (analysis of variance)

immunogenicity of porcine pancreatic islets for xenotransplantation. A study was undertaken of the Gal1-3Gal and Thomsen-Friedenreich (TF) antigens, which are the major xenoantigens responsible for hyperacute rejection by natural xenoantibodies in humans. There is evidence that cryopreservation of tissues or cells diminishes the expression of antigens, so prolonging graft survival.

Methods: The pancreases were obtained from adult White Large pigs (blood group O) and digested with collagenase (1 mg ml⁻¹) by the Ricordi semiautomated method. Some cells were fixed in formalin; others were cryopreserved in RPMI-1640 with 10 per cent dimethyl sulphoxide at a rate of -1°C per min to -70°C and stored at -196°C for 4 weeks. After thawing at 37°C, cells were fixed in formalin. Immunocytochemistry was carried out using human anti-Gal1-3Gal antibody eluted from a sepharose immunosorbent column and a mouse anti-TF monoclonal antibody.

Results: Both antigens were reduced after collagenase digestion and eliminated after cryopreservation. The Table shows the number of islets staining for the antigens.

State of islets	Gal1-3Gal	TF	P
Fresh			
Positive	136 (100)	113 (95)	
Negative	0 (0)	6 (5)	
Collagenase			
Positive	19 (17)	17 (14)	
Negative	93 (83)	102 (86)	<0.001*
Collagenase plus cryopreservation			
Positive	0 (0)	0 (0)	
Negative	123 (100)	119 (100)	<0.001†

Values in parentheses are percentages. *Collagenase *versus* fresh, †collagenase *versus* collagenase plus cryopreservation (χ^2 test)

Conclusion: The techniques of collagenase isolation and cryopreservation completely eradicate expression of the major xenoantigens in porcine islets. This finding may be important for clinical islet cell xenotransplantation.

Bactericidal/permeability-increasing protein attenuates the systemic inflammatory response syndrome in hind limb ischaemia-reperfusion

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Background: Hind limb ischaemia-reperfusion injury (IRI) increases gut permeability and the resultant endotoxaemia 'drives' a systemic inflammatory response syndrome (SIRS) leading to multiple organ dysfunction syndrome (MODS). Recombinant bactericidal/permeability-increasing protein (rBPI) is a novel antiendotoxin therapy with proven benefit in sepsis. This study examined its potential role in modulating endotoxin-induced SIRS in hind limb IRI.

Methods: Male Wistar rats ($n = 50$) were randomized into five groups: control and four groups undergoing 3 h bilateral hind limb ischaemia with 2 h reperfusion (I-R); intravenous rBPI was given to three groups at a concentration of 1 or 2 mg kg⁻¹ at reperfusion or 2 mg kg⁻¹ 1 h into reperfusion. Plasma interleukin (IL) 6 concentration was determined by bioassay as a measure of systemic inflammation. Biochemical markers of hepatic and renal function were also measured.

Results: Results in Table below.

Conclusion: These findings suggest that hind limb IRI produces SIRS, with an increase in IL-6 concentration and remote hepatorenal dysfunction. This inflammatory response can be modulated in part by rBPI antiendotoxin therapy, supporting the hypothesis that increased gut permeability and resultant endotoxaemia is 'the motor that drives' SIRS in this model. These results suggest that the attenuation is dose related and that optimal drug delivery may be at reperfusion.

Tumour-specific telomerase RNA expression in oesophageal and head and neck cancer is of potential clinical value

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Group	IL-6 (pg l ⁻¹)	Renal function		Hepatic function	
		Urea (mmol/L)	Creatinine (μ mol/l)	Bilirubin (μ mol/l)	ASAT (u/l)
Control	140.7(17.9)	6.1(0.9)	48.5(7.5)	5.8(0.2)	357.7(38.8)
I-R	1432.0(263.0)*	14.2(0.9)*	77.6(6.5)*	9.9(2.3)*	747.6(66.4)*
rBPI					
2 mg kg ⁻¹ at reperfusion	711.5(123.7)*†	14.2(0.9)*	81.3(12.7)*	11.8(1.5)*	756.4(113)*
1 mg kg ⁻¹ at reperfusion	821.9(108.3)*	13.0(1.7)*	>1200	13.3(2.4)*	>800
2 mg kg ⁻¹ 1 h after reperfusion	831.6(142.2)*	12.2(0.3)*	>1200	13.3(1.0)*	>800

Values are mean(s.e.m.) ASAT, aspartate aminotransferase. All parameters were increased significantly in the I-R groups *versus* control; * $P < 0.0001$,

† $P < 0.05$ *versus* I-R group

Background: Telomerase, the most common marker of the cancer cell, has detectable activity in 85 per cent of cancers but is largely repressed in normal tissues. Sequencing of its constituent human telomerase RNA (hTR) and protein components has demonstrated the role of telomerase in replicative senescence, immortality and neoplasia. In addition, it has permitted the manipulation of telomerase activity, especially inhibition of hTR, to provide a potential anticancer strategy. This study aimed to evaluate the frequency of hTR expression in oesophageal and head and neck squamous cell carcinoma (HNSCC), and to establish the potential therapeutic value of hTR inhibition by comparing the differential expression in malignant and normal tissue.

Methods: Formalin-fixed paraffin-embedded archival sections from 48 HNSCCs (floor of mouth (FOM), 23; tongue, 25) and from 47 oesophageal tumours (squamous cell carcinoma (SCC), 41; adenocarcinoma (ADC), 15, including nine paired endoscopic biopsy and surgical resection specimens) were examined using a radiolabelled riboprobe and given a positive or negative score for hTR expression. Results were compared with expression in controls and adjacent histologically normal tissue. Statistical analysis was with the χ^2 test; $P < 0.05$ was considered statistically significant.

Results: hTR was expressed in 76 per cent of HNSCCs (FOM 65 per cent *versus* tongue 88 per cent; $P = 0.61$) and in 54 per cent of oesophageal cancers (SCC 51 per cent *versus* ADC 60 per cent; $P = 0.56$). Frequency of hTR expression was significantly greater in HNSCC than in SCC oesophageal cancers ($P = 0.01$), but no significant difference in frequency of expression was found between HNSCC subsites, oesophageal SCC and ADC, nor histological grade in oesophageal tumours. Although not expressed in most normal surrounding tissue, occasionally hTR expression could be detected in the basal layer of squamous epithelium, but at a level below that of malignant tissue. Good correlation was found between frequency of expression in the paired oesophageal biopsy and resection specimens, with agreement in eight of nine paired specimens.

Conclusion: Tumour-specific expression of the essential hTR component of telomerase in both oesophageal and head and neck cancer confirms the potential for hTR inhibition as a clinically valuable therapeutic strategy. Biopsy specimens are representative of tumour hTR status, suggesting that biopsy may be the only tissue required to identify tumours for which this therapy is appropriate.

Clearance of circulating tumour cells in colorectal cancer is greatest in tumours with the best prognosis

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Background: Dukes staging of colorectal cancer remains the best prognostic indicator. An assessment was made of the relationship between the prevalence of circulating tumour cells

(CTCs) before and after operation and Dukes stage, using previously described methods based on reverse transcription-polymerase chain reaction (RT-PCR). The study aimed to determine whether a difference in the rate of CTC clearance correlates with Dukes stage.

Methods: Systemic venous blood was collected from patients with colorectal cancer undergoing treatment in two hospitals before operation and 24 h afterwards. RNA was extracted from the mononuclear cell fraction of the blood samples and subjected to RT-PCR using specific primers for carcinoembryonic antigen (CEA) messenger RNA (mRNA) and cytokeratin (CK) 20 mRNA. Healthy patients were used as 'no cancer' controls.

Results: CTCs were detected in 78 per cent of patients before operation, and there was no significant difference in pre-operative prevalence by Dukes stage.

Dukes stage	n	CEA or CK-20 positive		P
		Preop	24 h postop.	
Total	55	43 (78)	22 (40)	0.0001
A or B	38	28 (74)	10 (26)	0.0001
C	12	10 (83)	7 (58)	n.s.
'D'	5	5 (100)	5 (100)	n.s.

Values in parentheses are percentages. n.s., Not significant. *Fisher's exact test

There was a significant fall in the prevalence of CTCs 24 h after operation compared with values before surgery. Only the fall in patients with Dukes A or B disease was sufficiently large to reach significance on subgroup analysis by Dukes stage. Four of 85 'no cancer' controls were also positive.

Conclusion: CTCs can be identified before resection in the majority of patients with colorectal cancer regardless of Dukes stage, and are cleared from the circulation within 24 h of primary tumour removal. Clearance of circulating tumour cells in patients with colorectal cancer is greatest in tumours with the best prognosis and may indicate improved outcome.

Expression of NF- κ B but not of bcl-2 predicts response to neoadjuvant therapy in patients with oesophageal adenocarcinoma

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Background: Preoperative chemotherapy and radiation therapy improves outcome in patients with oesophageal adenocarcinoma. A molecular understanding of biological behaviour and tumour response or resistance to this neoadjuvant approach is awaited and may be of considerable clinical value. Programmed cell death is an important determinant of response to chemoradiotherapy and this study investigated

	NF- κ B		Bcl-2	
	Positive	Negative	Positive	Negative
Complete pathological response*	4	63†	42	26
Stage I+II disease*	12	30†	18	13
Median (range) survival (months)	7 (0–66)	12 (0–95)†	10 (1)	5 (0–66)†

*Values are percentages. † $P < 0.05$ (NF- κ B or bcl-2 negative *versus* NF- κ B or bcl-2 positive)

nuclear factor κ B (NF- κ B) and the antiapoptotic protein bcl-2, both key regulators of this process.

Methods: One hundred and ten patients with oesophageal adenocarcinoma had immunostaining for NF- κ B and bcl-2. Fifty-eight of the patients received neoadjuvant chemoradiotherapy and in these patients the pretreatment biopsies were also analysed.

Results: Increased levels of NF- κ B were found in 61 per cent of resected specimens and bcl-2 was expressed in 34 per cent. The correlation between expression of these markers and clinicopathological parameters is shown in the Table above.

Conclusion: The presence of bcl-2 and the absence NF- κ B expression is associated with significantly improved survival in patients with oesophageal adenocarcinoma. Only NF- κ B expression correlates with responsiveness to neoadjuvant therapy, which may prove useful in selecting patients who will benefit from this form of treatment.

Neoadjuvant chemoradiation does not alter the proangiogenic profile of oesophageal carcinoma

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Background: The prognosis of oesophageal carcinoma treated by surgery alone remains poor. Multimodal therapy involving preoperative chemoradiation significantly enhances survival in oesophageal adenocarcinoma but the majority of patients still die from metastatic disease. A recent study has identified tumour cells in the rib marrow of 88 per cent of patients with apparently curable disease. The growth of solid tumour metastases is dependent on the growth of new vessels. Raised levels of the circulating proangiogenic cytokines vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) have been reported in the serum of patients with certain malignancies. The significance of this increase and the effect of neoadjuvant therapy on the proangiogenic milieu are unclear. It was hypothesized that neoadjuvant chemotherapy would reduce the level of proangiogenic cytokines in patients with oesophageal cancer.

Methods: Three groups of patients were studied. Group 1 ($n = 22$) had neoadjuvant chemoradiotherapy followed by surgery for oesophageal cancer; group 2 ($n = 10$) had surgery alone for oesophageal cancer; and group 3 ($n = 17$) underwent

surgery for non-malignant conditions and acted as controls. Serum samples were taken at the time of diagnosis, during neoadjuvant therapy in group 1, and on days 1, 3 and 5 after operation in all three groups. Serum was assayed for VEGF and bFGF using an enzyme-linked immunosorbent assay.

Results: The mean(s.e.m.) serum VEGF concentration was 1157(71.5) pg ml⁻¹ in patients with oesophageal carcinoma compared with 294(28.2) pg ml⁻¹ in controls ($P < 0.02$). bFGF levels were not significantly increased and did not alter during treatment. Preoperative chemoradiotherapy had no effect on these indices. VEGF concentrations fell significantly on day 1 after tumour resection to 620(48.4) pg ml⁻¹ ($P < 0.05$), but had returned to preoperative levels by day 5.

Conclusion: Multimodal therapy does not alter the proangiogenic milieu for patients with oesophageal carcinoma. The effect of antiangiogenic strategies during neoadjuvant therapy and in the perioperative period needs to be examined.

Self-validating invasion assay for measurement of the effect of hyaluronate surgical coating solution

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Background: Intraperitoneal administration of agents has been postulated as a method for reducing the interaction between tumour cells and extracellular matrix components. CD44, a widely distributed adhesion molecule, has been implicated in the spread of epithelial tumours. The natural ligand for CD44 is hyaluronic acid (HA), and this has been employed to reduce postoperative adhesions. The aim of this study was to investigate the effects of viscous HA and the HA free carrier solution carboxymethylcellulose (CMC) on the invasion of human colonic cancer cells (SW1222) through reconstituted basement membrane (Matrigel) and synthetic filters.

Methods: Twelve-well plates with 3- μ m filter inserts were coated with Matrigel (100 μ m cm⁻²) and allowed to set. Ten wells were then coated with 120 μ l viscous HA, ten with 120 μ l CMC and ten with 120 μ l phosphate-buffered saline as a control. After an incubation period of 1 h, the tops of the wells were seeded with 1×10^5 cells as a single cell suspension and the lower parts of the wells were filled with 1 ml phenol-free RPMI medium. All the plates were incubated for 48 h at 37°C. The well inserts were then removed and the Matrigel was

cleaned from the filters with cotton buds. The filters were returned to the wells and a methyl tetrazolium salt (MTS) assay was performed on all wells. The absorbency was read after 2 h at 490 nm. After this period the insert filters were excised and stained for cells with haematoxylin and eosin. The stained filters were mounted on slides and scanned on a computer. The density of the colours on the slides was measured.

Results:

	Control	CMC	HA
Relative invasiveness (%)	100	52.4*	38.1†
Density reading	1	0.86†	0.82†

* $P < 0.01$, † $P < 0.001$

These two methods of measuring the degree of cancer cell invasion show that it is significantly decreased by both HA and CMC. In the MTS assay, HA decreased cancer cell invasion more than CMC.

Conclusion: This study demonstrated a method of measuring cancer cell invasion *in vitro* using two methods in one study. It was also shown that a viscous fluid will decrease cancer cell invasion *in vitro* and that viscous HA decreases this further. Viscous HA could be administered to decrease invasion of shed cancer cells at operation.

Taurolidine inhibits tumour cell growth *in vitro* and *in vivo*

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Background: Taurolidine, a derivative of the amino acid taurine, exhibits antiendotoxin and antibacterial effects, and has been used both locally and systemically in the treatment of patients with peritonitis. It also demonstrates antiadherence activity towards micro-organisms in the peritoneal cavity. Taurolidine may have antiproliferative effects on tumour cells. This study aimed to examine the effect of taurolidine on the growth of a rat metastatic colorectal tumour cell line (DHD/K12/TRb) *in vitro* and *in vivo*.

Methods: In the first experiment DHD/K12/TRb cells were incubated with 5, 10, 15, 25, 250 and 500 $\mu\text{g ml}^{-1}$ taurolidine. Cells incubated in culture medium alone were used as controls. Cell proliferation was assessed by means of 5-bromo-2-deoxyuridine labelling. Cell viability was measured using the Cell Titre 96 Aqueous One Solution Proliferation assay. Cell death was quantified using the lactate dehydrogenase (LDH) cytotoxicity assay. In the second experiment, BD IX rats were randomized into two groups (six animals per group). Group 1 (control) underwent laparotomy, instillation of DHD/K12/TRb tumour cells intraperitoneally followed by phosphate-buffered saline (PBS). Group 2 received taurolidine 100 mg kg^{-1} instead of PBS. Animals were killed after 24 days and the

	Proliferation (%)	Cell viability (%)	LDH cytotoxicity (%)
Control	100(28)	100(17)	100(26)
Taurolidine ($\mu\text{g ml}^{-1}$)			
5	24(5)*	77(12)*	180(40)*
10	25(4)*	63(7)*	233(65)*
15	25(4)*	56(9)*	226(79)
25	18(5)*	41(8)*	403(28)*

Values are mean(s.d.). * $P < 0.05$ versus control value (taken as 100 per cent) (Student's *t* test)

tumour burden was assessed by counting the number of tumour nodules in the peritoneal cavity.

Results: Incubation of the tumour cells with taurolidine resulted in a fourfold decrease in proliferation rates and a fourfold increase in cell necrosis as demonstrated by the increase in LDH release at a taurolidine concentration of 25 $\mu\text{g ml}^{-1}$. A dose-dependent decrease in cell viability was also observed. In the *in vivo* study, local taurolidine administration resulted in a significant decrease in mean(s.d.) tumour burden (4(2) nodules in group 2 animals versus 586(182) nodules in group 1 animals; $P < 0.05$).

Conclusion: Taurolidine inhibits the growth of a rat metastatic colorectal tumour cell line *in vitro* and *in vivo*, and thus may have potential in the treatment of peritoneal metastases.

Experimental study of mitomycin C disposition after intraperitoneal administration of the drug adsorbed to activated charcoal

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Background: Preoperative instillation of mitomycin C (MMC) adsorbed on to activated carbon (MMC-AC) for sustained drug release has been proposed as a therapy to prevent peritoneal recurrence after gastrectomy for cancer.

Methods: The adsorption, pharmacokinetics and tissue distribution properties of MMC-AC in rats were investigated, comparing two different carbon particle sizes (53–75 and 150–180 μm) with MMC alone.

Results: The mean(s.e.m.) plasma half-life of MMC-AC was 146(56) min versus 62(24) min for MMC. The area under the curve was lower for MMC-AC at 4 h (805(182) versus 321(169)), indicating sustained MMC release beyond this point. The times to peak plasma concentrations were similar for MMC-AC and the control, but the charcoal preparation resulted in lower peak plasma concentrations of MMC (7.7(1.7) versus 2.2(0.8) $\mu\text{g ml}^{-1}$; $P < 0.05$, *t* test). Plasma, blood and peritoneal fluid MMC profiles demonstrated rapid drug equilibration between compartments. MMC-AC targeted the peritoneum and lymphatic system; peritoneal lymph nodes, omentum and spleen displayed the highest peak drug concentrations. MMC concentrations peaked in peritoneal

lymph nodes at 40 min and were 20-fold higher than in axillary lymph nodes, where the peak was at 4 h. MMC adsorption and plasma pharmacokinetics were independent of activated charcoal particle size, but the larger particles were preferentially retained locally.

Conclusion: MMC-AC shows properties suitable for a locally administered agent to suppress peritoneal metastasis from gastric cancer.

Case-control study of symptom patterns in patients with oesophagogastric cancer

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Background: A better understanding of the patterns of 'dyspeptic' symptoms associated with a high risk of gastric and oesophageal cancers would help to target endoscopy resources more appropriately.

Methods: A case-control study by structured interview was performed to assess the nature, duration and persistence of symptoms in 63 patients recently treated for oesophagogastric cancer. Two control groups were also studied: (1) control A – patients attending for endoscopy which demonstrated normality or benign disease; and (2) control B – people aged over 40 years in the local population who described recent dyspeptic symptoms. Two age- and sex-matched individuals from each control group were assigned to each case.

Results:

	No. of patients with cancer	Control A	Control B
Median duration of symptoms (months)	5	18	60†
Percentage with continuous symptoms	40‡	22	8*‡

* $P < 0.001$, † $P < 0.00001$ (χ^2 test). ‡Likelihood ratio 4.21

Eighty-two per cent of patients with cancer, 58 per cent of control A patients and 14 per cent of control B patients had symptoms for less than 1 year. Patients with cancer were more likely to suffer from dysphagia and anorexia than controls: $P < 0.01$ versus control A ($\chi^2 = 6.7$); $P < 0.001$ versus control B ($\chi^2 = 15.4$).

Conclusion: Patients aged over 40 years with continuous symptoms, a history of less than 1 year and a history of anorexia or dysphagia are considerably more likely to have cancer than other dyspeptic patients.

Rise in levels of angiogenic growth factors is associated with venous thrombus resolution

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Background: The enhancement of deep vein thrombus resolution may reduce debilitating long-term complications. Resolution is analogous to wound healing, with angiogenesis leading to recanalization. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are important angiogenic factors and may play a role in thrombus recanalization and resolution. This study aimed to investigate VEGF and bFGF expression during resolving venous thrombosis.

Methods: Thrombi were induced in a rat inferior vena cava (IVC) by creating a stenosis to reduce blood flow by 80–90 per cent. Laminated thrombi were reliably produced (median weight at 1 day was 39 (range 23–63) mg). Thrombi, adjacent IVC tissue and serum were collected at 1, 3, 7, 14, 21 and 28 days (groups of nine). Tissue results are expressed as picograms per milligram of soluble protein. The study was performed with Home Office approval.

Results: There was a significant increase in thrombus VEGF concentration between day 1 (median 247 (range 0–514) pg mg⁻¹) and day 7 (556 (254–1741) pg mg⁻¹) ($P = 0.02$, Mann-Whitney U test). Considerable variation was seen in VEGF concentration between days 14 and 28 (range 0–7726 pg mg⁻¹) with no significant difference between day 7 and subsequent days. There was a positive correlation between thrombus bFGF concentration and time ($r = 0.74$, $P < 0.0001$), with a greater than 300-fold increase in bFGF concentration from day 1 (median 1.1 (range 0.38–5.37) pg mg⁻¹) to day 28 (349 (198–1059) pg mg⁻¹). VEGF (160 (0–2731) pg mg⁻¹) and bFGF (311 (116–884) pg mg⁻¹) concentrations in the adjacent IVC did not significantly change with time. Serum VEGF levels were raised significantly at days 1 and 3 (day 1+3 median 4732 (range 2564–7912) pg ml⁻¹) and were reduced thereafter (days 7–28 median 1524 (range 0–3656) pg ml⁻¹) ($P < 0.0001$, Mann-Whitney U test). Serum bFGF concentration did not change with time (median 15 (range 1–46) pg ml⁻¹).

Conclusion: VEGF and bFGF are found in organizing thrombi and have characteristic temporal expression patterns suggesting a role in resolution. Serum levels of VEGF are raised for up to 3 days after thrombus formation. Therapeutic manipulation of angiogenic growth factor expression may enhance recanalization and reduce the long-term complications of thrombosis.

Endothelin receptors in critical limb ischaemia

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Background: Circulating levels of endothelin (ET) 1, a potent vasoconstrictor peptide, are reportedly raised in patients with atherosclerotic disease. Two principal ET-1 receptor subtypes have been identified, designated ET_A and ET_B. This study examined the expression of endothelin receptors in the muscle microvessels of patients with chronic critical limb ischaemia (CLI) as a potential mechanism in the pathophysiology of peripheral vascular disease.

	Controls (n=9)	CLI (n=16)	P*
ET-1	29.9(4.4)	59.6(4.8)	<0.001
ET _A receptor	2.1(0.5)	6.2(0.7)	<0.001
ET _B receptor	3.8(0.6)	6.9(0.7)	<0.01

Values are mean(s.e.m.) radioligand binding, expressed as d.p.m. $\times 10^3$ activity mm^{-2} . *Student's *t* test

Methods: Calf muscle biopsies were obtained from patients undergoing surgical intervention for CLI. Control biopsies were obtained from patients having operation for minor varicose veins. Autoradiography for ET-1 and endothelin receptor subtypes was performed on slide-mounted sections. Sections were incubated in ^{125}I -labelled ET-1, and ET_A/ET_B binding sites were identified using subtype-selective radioligands. Autoradiographs were quantified by densitometry. Microscopic localization of binding was achieved using nuclear emulsion. Additionally, serum levels of ET-1 were measured in the patients with CLI and compared with those of an age- and sex-matched cohort.

Results: Mean(s.e.m.) serum levels of ET-1 were raised in patients with CLI compared with controls (1.7(0.3) *versus* 0.9(0.1) pg ml^{-1} ; $P < 0.02$, Student's *t* test). The increase in ET-1 binding in the muscle microvessels of patients with CLI reflects a significant increase in the expression of both ET_A and ET_B receptor subtypes.

Conclusion: Raised levels of circulating ET-1 may contribute to the pathophysiology of CLI via actions on endothelin receptors, expressed on skeletal muscle microvessels.

Low molecular weight heparin, enoxaparin, attenuates leucocyte rolling and adhesion induced by ischaemia-reperfusion

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Background: Leucocyte adhesion and migration plays a central role in microvascular injury during ischaemia-reperfusion (I-R). Unfractionated heparin has been demonstrated to diminish this response. Recent studies suggest that low molecular weight heparin may not be as effective. The aim of this study was to investigate the effect of enoxaparin, a low molecular weight heparin on I-R-induced leucocyte-endothelium interactions by using intravital videomicroscopy.

Methods: Sprague-Dawley rats were randomized into three groups: saline plus I-R, heparin plus I-R, and enoxaparin plus I-R. I-R injury was established by occlusion of the superior mesenteric and coeliac vascular pedicle for 10 min, followed by 60 min of reperfusion. Saline, heparin and enoxaparin (100 units per kg body-weight as a bolus in both) were administered 10 min before I-R and infused during the I-R period. The number of adherent and migrated leucocytes, and their rolling velocity, were measured by intravital microscopy

	Saline + I-R	Heparin + I-R	Enoxaparin + I-R
60 min reperfusion			
Rolling velocity ($\mu\text{m s}^{-1}$)	31.8(2.2)*	37.9(4.3)	43.9(2.2)
No. adherent (per 100 μm)	17.9(2.1)*	12.1(3.0)	5.2(1.1)
No. migrated (per field)	9.1(2.4)	6.4(2.5)	3.1(0.3)

Values are mean(s.e.m.). * $P < 0.05$ *versus* enoxaparin + I-R (analysis of variance with Scheffé *post hoc* test)

in a postcapillary venule at baseline (−10 min), ischaemia (0 min) and 10, 30 and 60 min after reperfusion.

Results: I-R significantly increased the number of adherent and migrated leucocytes at 60 min and decreased the rolling velocity of leucocytes at 10, 30 and 60 min after reperfusion. Administration of enoxaparin significantly attenuated the decrease in leucocyte rolling velocity and the increase in leucocyte adhesion after reperfusion. Heparin did not alter this response.

Conclusion: These data demonstrate that, contrary to earlier reports, low molecular weight heparins are effective in reducing leucocyte-endothelial interactions after I-R.

Antioxidant glutathione peroxidase protects against oxidative injury in complex hind limb ischaemia-reperfusion injury

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Background: Complex limb trauma involves both major arterial and venous injury, and subsequent reperfusion is often complicated by delayed restoration of venous outflow. Antioxidant depletion and the resultant oxidative injury are important in pure arterial ischaemia-reperfusion injury (IRI). The role of antioxidant status in a model of combined vessel injury with delayed venous reflow was investigated.

Methods: New Zealand White rabbits ($n=18$) were randomized into three groups. The control group underwent a sham groin exposure and two groups underwent unilateral hind limb arterial and venous occlusion for 1 h, followed by arterial

	Plasma glutathione peroxidase concentration (units l^{-1})		
	Systemic vein		Femoral vein (endpoint)
	Start	Endpoint	
Control	414.8(31.7)	391.4(33.4)	440.1(47.2)
No treatment	468.0(41.2)	412.2(35.6)	358.4(22.0)*
Treatment	607.8(36.3)†	562.3(40.6)†	547.2(24.9)†‡

Values are mean(s.e.m.). * $P < 0.05$, † $P < 0.01$ *versus* control; ‡ $P < 0.005$ *versus* no treatment

reperfusion alone for 1 h, followed by arterial and venous (delayed) reflow for 1 h. One of the ischaemia-reperfusion groups was pretreated with an enteral combination antioxidant vitamin supplement, containing selenium, methionine and vitamins A, C and E. Plasma hydroperoxide concentrations (to measure oxidative injury) and glutathione peroxidase levels (to measure antioxidant capacity) were assayed in both the femoral vein and a systemic vein.

Results: Mean(s.e.m.) plasma hydroperoxide concentrations in the femoral vein were significantly greater ($2.0(0.5) \mu\text{mol l}^{-1}$, $P < 0.05$) in the delayed venous reflow group, but not in the antioxidant-pretreated group ($1.3(0.3) \mu\text{mol l}^{-1}$) compared with the control group ($1.0(0.1) \mu\text{mol l}^{-1}$).

Conclusion: In this model combined vessel temporary occlusion with delayed venous reflow was associated with antioxidant depletion and evidence of oxidative injury in the limb. Pretreatment with antioxidant vitamins enhances glutathione peroxidase levels and prevents local limb lipid peroxidation.

Induction of thermotolerance preserves endothelial vasomotor function after ischaemia-reperfusion *in vivo*

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Background: Ischaemia-reperfusion (I-R) results in endothelial dysfunction, seen as a loss of endothelium-dependent vasodilatation. In prolonged ischaemia the end-result can be marked vasospasm or 'no reflow' (failure to observe forward flow in a mesenteric arteriole). Thermotolerance attenuates I-R-induced microvascular injury. The aim of this study was to investigate the effect of thermotolerance on I-R-induced vasomotor changes and 'no reflow'.

Methods: Endothelium-dependent and -independent vasodilatation, measured by response to acetylcholine and sodium nitroprusside respectively, was measured in mesenteric arterioles ($27.5\text{--}38 \mu\text{m}$) by intravital microscopy. Sprague-Dawley rats were randomized into an untreated group (IR group, $n = 12$) and a group in which thermotolerance was induced (TIR, $n = 12$). Vasomotor function was measured by the arteriolar constriction:dilatation (C:D) ratio. Thermotolerance was induced 18 h before I-R injury by increasing core body temperature to $41 \pm 0.5^\circ\text{C}$ for 15 min. The I-R injury

	C:D ratio	
	Endothelium dependent	Endothelium independent
Baseline	2.1(0.2)	2.1(0.2)
IR group	1.4(0.3)*	2.1(0.2)†
TIR group	2.0(0.2)‡	2.0(0.2)

Values are mean(s.d.). * $P < 0.01$ versus baseline, ‡ $P < 0.01$ versus IR, † $P < 0.01$ versus endothelium-dependent C:D ratio (analysis of variance with Scheffé *post hoc* correction for vasomotor parameters and χ^2 test for no-reflow rate)

involved occlusion of the superior mesenteric and coeliac vascular pedicle for 30 min followed by 60 min reperfusion. The arteriolar blood flow and 'no reflow' phenomenon were measured by intravital microscopy.

Results: I-R caused a significant decrease in endothelium-dependent vasodilatation as measured by response to acetylcholine. Endothelium-independent dilatation was preserved ($2.1(0.2)$ versus endothelium-dependent vasodilatation, $P < 0.01$). Thermotolerance prevented this decrease in endothelium-dependent vasodilatation ($P < 0.01$ versus acetylcholine). In this model I-R caused a 'no reflow' phenomenon in 16 of 24 rats. Thermotolerance significantly reduced this 'no reflow' to four of 16 rats ($P < 0.05$).

Conclusion: Preconditioning by thermotolerance preserves endothelial vasomotor function and markedly reduces 'no reflow' in arterioles. Further investigations of the precise mechanism by which thermotolerance preserves endothelial function are necessary.

Thromboelastography is a simple screen for hypercoagulable states and a good predictor of failure following peripheral arterial intervention

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Background: Undetected coagulation abnormalities may cause unexpectedly early bypass graft or angioplasty failure. Screening for known hypercoagulable factors is expensive and slow. Thromboelastography (TEG) provides a global assay of clotting and is used routinely in liver transplantation and cardiac surgery. The aim of this study was to investigate the role of TEG in screening for hypercoagulability and in predicting interventional failure in lower limb arterial disease.

Methods: Seventy-two people underwent TEG, comprehensive thrombophilia screening and fibrinogen assays. Fifty-two were patients, with a mean age of 69 (range 34–90) years, and 20 were normal healthy controls aged 49 (20–74) years. All patients were admitted with chronic limb ischaemia between December 1998 and March 1999.

Results: Analysis of TEG findings showed that 26 (50 per cent) of the 52 patients were hypercoagulable compared with three (15 per cent) of the 20 controls ($P < 0.01$). Thrombophilia screening detected one or more defects in 11 (21 per cent) of patients (lupus anticoagulant, five; protein C deficiency, three; protein S deficiency, four; factor V Leiden, two) but none in controls. Fibrinogen levels were increased in 12 (23 per cent) of the patients and in three (15 per cent) controls, all of whom had a hypercoagulable TEG finding. Hypercoagulable TEG traces were found in all but one patient with a positive thrombophilia screen. Ten patients with normal fibrinogen and thrombophilia screens had a hypercoagulable TEG trace, of whom four had a failed intervention at 3-month follow-up. Overall, TEG hypercoagulability was a better predictor of interventional failure than either thrombophilia screening or fibrinogen assay.

After a mean follow-up of 3 months, 43 (83 per cent) of the 52 patients had undergone urgent interventions. Of these, ten (23 per cent) had occluded within 3 months. TEG was the most sensitive test for detecting early failure in these patients (eight of ten were TEG hypercoagulable, two of ten had a thrombophilia abnormality and three of ten had a raised fibrinogen level).

Conclusion: TEG is a quick and simple method for detecting hypercoagulability before intervention and is a better predictor of early interventional failure than more complex thrombophilia screens.

Cationic trypsinogen gene mutations: relevance in non-hereditary chronic pancreatitis

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Background: Cationic trypsinogen gene mutations have been identified in patients with hereditary pancreatitis. A mutation in exon 3 (R117H) produces an arginine (CGC) to histidine (CAC) substitution resulting in an inactivation-resistant trypsin. This study aimed to investigate the relevance of this mutation in patients with alcoholic and idiopathic chronic pancreatitis (CP).

Methods: DNA was extracted from blood samples of 40 patients with CP, 20 normal, ethnically matched controls and 20 alcoholic controls (alcoholics without pancreatitis). Of the patients with CP, 27 were of alcoholic aetiology and 13 were idiopathic. The R117H mutation was examined by restriction endonuclease (*Afl*III) digestion of polymerase chain reaction products.

Results: The R117H mutation was detected in one of the alcoholic patients with CP. It was not detected in the idiopathic CP group, nor in the control groups.

Conclusion: Screening for cationic trypsinogen gene mutations may be of relevance in patients with non-hereditary CP and their families. Further studies are required to determine the prevalence of this mutation in CP, irrespective of aetiology.

Meta-analysis of the efficacy of acid-reducing agents in the management of patients with peptic ulcer haemorrhage

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Background: The management of peptic ulcer haemorrhage continues to pose questions and provoke controversy, especially with respect to the use of acid-reducing agents. Most clinical trials examining the efficacy of these drugs contain small numbers of patients, making it difficult to draw conclusions about their efficacy. This report is a meta-analysis aimed at examining the effects of acid-reducing drugs in the management of peptic ulcer haemorrhage.

Methods: Studies were located using a search of the Medline database between 1980 and 1999. All the 21 studies selected were published in English, and randomized and controlled by a placebo group. The Mantel-Haenszel and random models were used in conducting the statistical processes of this meta-analysis.

Results: The 21 trials included a total of 3566 patients and the mean study size was 170 (range 20–1005). Seventeen of the papers assessed the efficacy of H₂ antagonists, three assessed proton pump inhibitors, and one was concerned with antacid therapy. The meta-analysis showed a significant reduction in the odds ratio for rebleeding rate (0.727 (range 0.618–0.855), $P < 0.001$) and operation rate (0.707 (0.582–0.859), $P < 0.001$) but not for mortality rate (1.140 (0.818–1.588), $P = 0.49$) when acid-reducing agents were used for acute peptic ulcer haemorrhage.

Conclusion: This meta-analysis demonstrated a significant beneficial effect of acid-reducing agents in reducing rebleeding and operation rates.

Impact of laparoscopic antireflux surgery on quality of life

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Background: Laparoscopic antireflux surgery is aimed at improving quality rather than quantity of life for patients with gastro-oesophageal reflux disease (GORD). The Short-Form 36 (SF-36) is a well validated questionnaire that measures eight important health concepts (domains): physical function (PF), role – physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role – emotional (RE) and mental health (MH). This study aimed to assess formally the quality of life (QoL) as an independent outcome measure in the evaluation of patients with GORD undergoing laparoscopic antireflux surgery.

Methods: SF-36 questionnaires were given to patients before laparoscopic antireflux surgery. Patients were asked to complete and return further SF-36 questionnaires at 6-month intervals after operation. The preoperative scores for each domain and those at 6 and 24 months after operation were analysed with the Mann-Whitney *U* test.

Results: Data were collected from 75 patients; the Table shows the median score for each domain. Data from a published

SF-36 domain	PF	RP	BP	GH	VT	SF	RE	MH
'Normal' population	84	83	77	70	59	87	82	72
Preop.	68	50	46	55	55	58	100	68
6 months postop	90†	100†	82†	70†	65†	78†	100	80*
24 months postop	95†	100†	93†	57	50	80†	100	76

* $P < 0.05$, † $P < 0.01$ versus preop. score (Mann-Whitney *U* test)

'normal' local population, corresponding to the median age of the patients, are shown as a reference, but no statistical comparison has been made.

Conclusion: Laparoscopic antireflux surgery is capable of producing sustained patient benefit in terms of improvement in QoL for patients with GORD. Highly significant improvement occurred in PF, RP, BP, GH, VT and SF domains when assayed by the SF-36 at 6 months. These effects were still evident in most domains after 2 years.

Nasogastric intubation causes gastro-oesophageal reflux in patients undergoing elective laparotomy

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Background: The routine use of nasogastric tubes in patients undergoing elective abdominal surgery is associated with an increased incidence of postoperative fever, atelectasis and pneumonia. Previous studies have shown that nasogastric tubes have no significant effect on the incidence of gastro-oesophageal reflux (GOR) or on lower oesophageal sphincter (LOS) pressure in healthy volunteers. It was hypothesized that nasogastric intubation in laparotomy patients reduces LOS pressure and promotes GOR in the perioperative period.

Methods: A prospective case-control study was undertaken in which 15 consenting patients admitted electively for bowel surgery were randomized into two groups. Patients in group 1 underwent nasogastric intubation after induction of anaesthesia and those in group 2 did not. All patients had manometry and pH probes placed under endoscopic vision, at the LOS and distal oesophagus respectively. Nasogastric tubes, where present, were left on free drainage, and sphincter pressures and pH were recorded continuously over a 24-h period. Data were analysed by means of analysis of variance.

Results: The mean number of reflux episodes (defined as pH less than 4) in the nasogastric tube group was 137 compared with 8 in the group managed without a nasogastric tube ($P=0.006$). The mean duration of the longest episode of reflux was 138 min in group 1 and 8 min in group 2 ($P=0.001$). A mean of 13.3 episodes of reflux lasted longer than 5 min in group 1, with pH less than 4 for 37.4 per cent of the 24 h; in comparison, patients in group 2 had a mean of 0.1 episodes lasting longer than 5 min ($P=0.001$) and pH was less than 4 for 0.2 per cent of the total time ($P=0.001$). Mean LOS pressures were lower in group 2.

Conclusion: These findings demonstrate that, unlike healthy subjects, patients undergoing elective laparotomy with routine nasogastric tube placement have significant GOR in the perioperative period and a reduced ability to clear acidic material from the distal oesophagus. Because of the associated risk of postoperative pulmonary complications, it is recommended that nasogastric intubation be performed selectively rather than routinely.

PRSS1 mutations in patients with hereditary pancreatitis in Europe and their relationship to disease presentation and progression

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Background: Hereditary pancreatitis (HP) causes recurrent attacks of acute pancreatitis, resulting in chronic pancreatitis, endocrine and exocrine failure. Two mutations have been identified in the gene coding for protease serine 1 (*PRSS1*), which is one of the genes underlying this condition. The R117H mutation results in an arginine to histidine substitution at position 117 in exon 3, and the N211 mutation is an asparagine to isoleucine transition at position 21 in exon 2. This study aimed to determine the incidence of *PRSS1* mutations in Europe and to identify the phenotypic expression of the two mutations.

Methods: The European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC) was established with full ethical approval in 1997. After informed consent, both affected and unaffected family members were tested for the two mutations. R117H was detected by restriction enzyme digestion of exon 3 with *AflIII*, which recognizes the mutation site. Mutation-specific primers were used to identify the N211 mutation. Clinical and epidemiological information was obtained from both the referring clinician and the patient, and was correlated with the patient's mutation status. Statistical analysis was with the Mann-Whitney *U* test.

Results: Ninety-nine families have been referred to EUROPAC. Of those tested, 26 families (80 patients) tested positive for the R117H mutation and 16 families (44 patients) for the N211 mutation; 22 families (32 patients) had neither mutation. The sex distribution of R117H and N211 patients was 45 per cent male ($n=35$) and 55 per cent female ($n=41$). The age at onset of symptoms of pancreatitis was no different between the R117H group and the N211 group (12.0 (range 10.0–17.6) versus 11.5 (10.4–17.6) years respectively, $P=0.8$). The R117H group had significantly more symptomatic episodes per year: 3.0 (2.6–4.3) versus 1.0 (0.9–2.4) attacks ($P=0.003$). Despite these findings, patients in the N211 group developed diabetes mellitus earlier during the course of the disease than those in the R117H group (13 (5.1–18.2) versus 25 (17.5–30.1) years, $P=0.008$). The age of development of malabsorption from symptom onset was identical between the two groups (11.0 (4.7–21.1) versus 11.5 (7.2–23.0) years, $P=1.0$). A higher proportion of the patients with the N211 mutation required surgical intervention for complications of HP: 15 (41 per cent) of 37 compared with 19 (33 per cent) of 57 in the R117H group.

Conclusion: Patients in the R117H group reported a higher number of symptomatic episodes of pancreatitis than those in

the N211 group. This did not result in a higher rate of complications of chronic pancreatitis or an increase in the number of operative procedures.

Experimental study of cytosolic calcium and intracellular enzyme activation in pancreatic acinar cells

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Background: The intracellular event that initiates acute pancreatitis is unknown. Disruption of the normal processes of calcium signalling has been shown to occur early in the pathogenesis of this condition. This study tested the hypothesis that the early intracellular events of acute pancreatitis are triggered by abnormal increases in the level of free ionized cytosolic calcium ($[Ca^{2+}]_i$) within the acinar cell.

Methods: Isolated mouse pancreatic acinar cells were treated with cholecystokinin (CCK) 10 nmol l^{-1} (for hyperstimulation) or thapsigargin $2 \text{ } \mu\text{mol l}^{-1}$ (for calcium store depletion) in order to generate increases in $[Ca^{2+}]_i$ by two separate mechanisms. Preloading with the specific calcium chelator 1,2-bis(2-aminophenoxy)ethane-N,N',N'-tetra-acetic acid (BAPTA) was used to attenuate the $[Ca^{2+}]_i$ rise. Calcium measurements were performed using Fura-2. Intracellular activation of trypsin was visualized simultaneously using the fluorescent substrates bis(ile-pro-arg)-rhodamine 110 and ile-pro-arg-7-amino-4-chloromethylcoumarin. Soybean trypsin inhibitor was used in all experiments to suppress extracellular cleavage of substrate.

Results: CCK and thapsigargin both induced increases in $[Ca^{2+}]_i$ to mean(s.e.m.) peaks of $591(29)$ and $384(18) \text{ nmol l}^{-1}$ respectively, followed by plateau increases of $31(3)$ and $45(7) \text{ nmol l}^{-1}$ which were prolonged for up to 60 min. Some 300 s after initiation of the abnormal calcium signal there was a visible increase in intracellular fluorescence from cleavage of the trypsin substrate. This fluorescence could be quenched immediately by addition of the cell-permeable trypsin inhibitor, benzamidine. No enzyme activation was seen on treatment of cells with buffer solution alone or with physiological doses of CCK (less than 50 pmol l^{-1}). Pretreatment of the cells with BAPTA to suppress the $[Ca^{2+}]_i$ rise prevented enzyme activation from both CCK and thapsigargin. Confocal microscopy showed trypsin activation to be occurring in discrete intracellular compartments at the secretory pole of the cell, within the granular region.

Conclusion: These data indicate that abnormal increases in $[Ca^{2+}]_i$ trigger intracellular enzyme activation, and suggest that such increases in $[Ca^{2+}]_i$ may be the trigger for acute pancreatitis.

Non-genomic effects of oestrogen on sodium hydrogen exchange: a mechanism for mitogenesis

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Background: Oestrogen is an important mitogen in epithelial cancers; more than 60 per cent of such tumours express oestrogen receptors. A rapid upregulation has been found in membrane sodium-hydrogen exchange (NHE) by oestrogen in rat tissue, which occurs distinct from the traditional receptor. It has been suggested that NHE activity accompanies growth stimuli as a signal for mitogenesis. This study investigated the hypothesis that oestrogen rapidly alters NHE activity and nuclear kinetics.

Methods: Crypts were isolated from human distal colon by calcium chelation. The colonic cancer cell line T84 was used as a model of tumour activity. NHE activity was measured by spectrofluorescence imaging of a pH-sensitive intracellular probe, bis(carboxyethyl)carboxyfluorescein (BCECF). DNA replication activity was measured by $[^3\text{H}]$ thymidine incorporation over 12 h. Gene-directed protein synthesis was inhibited with cycloheximide $1 \text{ } \mu\text{g ml}^{-1}$ in all experiments. NHE and protein kinase C (PKC) were inhibited with ethylisopropylamiloride $10 \text{ } \mu\text{mol l}^{-1}$ and chelerythrine chloride $1 \text{ } \mu\text{mol l}^{-1}$ respectively. Mean(s.e.m.) values are given for oestrogen 1 nmol l^{-1} , where $n=6$ crypts or $n=3 \times 10^5$ tumour cells. The Mann-Whitney *U* test was used for statistical analysis.

Results: Oestrogen induced a cellular alkalinization of crypts (pH change $0.19(0.06)$; $P<0.001$) and cancer cells (pH change $0.21(0.04)$; $P<0.001$) within 15 min that was sensitive to NHE inhibition ($P<0.01$). PKC inhibition blocked this activation of NHE in crypts (pH change $0.06(0.01)$; $P<0.05$) and cancer cells (pH change $0.09(0.02)$; $P<0.05$). Oestrogen increased DNA replication by 38 per cent ($14024.6(323.1)$ versus $10158.2(211.8)$; $P<0.01$) and this was similarly reduced by inhibiting NHE (3 per cent; $P<0.01$) or PKC (13 per cent; $P<0.05$).

Conclusion: Oestrogen rapidly activates NHE and stimulates DNA replication in normal and cancer cells in a mechanism that is mediated by PKC rather than gene-directed protein synthesis. This study provides evidence that oestrogens exert mitogenic influences via a non-genomic receptor that has yet to be fully characterized.

Fibrosis after renal ischaemia-reperfusion injury is associated with decreased matrix degradation

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Background: Renal ischaemia-reperfusion injury (IRI) is an inevitable consequence of transplantation and contributes to later graft fibrosis associated with chronic allograft nephropathy. This study aimed to elucidate the possible mechanisms behind this by looking at the expression of genes associated with fibrosis.

Methods: Male Wistar rats were used in this experiment, which had Home Office approval. Experimental groups (IRI, $n=6$ per time point) underwent laparotomy clamping of the right renal pedicle with a spring-clip for 45 min and left nephrectomy. Control groups ($n=4$ per time point) underwent left

	TGF- β		TIMP-1		Collagen III	
	Control	IRI	Control	IRI	Control	IRI
8 weeks	0.63(0.09)	0.78(0.08)	0.42(0.05)	0.43(0.08)	2.10(0.17)	1.11(0.13)†
16 weeks	0.58(0.11)	0.97(0.12)*	0.37(0.03)	0.48(0.03)	2.22(0.22)	1.38(0.35)
24 weeks	0.94(0.11)	1.38(0.16)	0.42(0.03)	0.65(0.04)†	1.90(0.14)	2.09(0.57)

Values are mean(s.e.m.). TGF- β , transforming growth factor β ; TIMP-1, tissue inhibitor of metalloproteinase 1. * $P < 0.05$, † $P < 0.01$ versus control (Students' *t* test)

nephrectomy only. Animals were killed at 8, 16 and 24 weeks and renal tissue was snap-frozen. Messenger RNA (mRNA) was extracted and genes of interest were amplified by reverse transcription-polymerase chain reaction, then quantified in an enzyme-linked immunosorbent assay system. Levels were expressed as a ratio with a known housekeeping gene, *GAPDH*. **Results:** Levels of TGF- β and TIMP-1 were increased at 16 weeks following injury and this increase was sustained. Interestingly, collagen III mRNA levels fell initially but had returned to normal by 24 weeks.

Conclusion: These results suggest that the fibrosis associated with renal IRI is likely to result from decreased matrix degradation due to inhibition of proteolytic enzymes, rather than increased collagen production.

Herbimycin A reduces intimal hyperplasia in a carotid balloon injury model

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Background: Intimal hyperplasia is a major cause of restenosis following endovascular procedures. Induction of cytoprotective heat shock proteins (HSPs) by thermal preconditioning has been shown to protect against intimal hyperplasia in the rat carotid balloon injury model. Thermal preconditioning has limited clinical applications, and an equally effective pharmacological HSP inducer would be more advantageous. Herbimycin A is a tyrosine kinase inhibitor and a known HSP inducer. It was hypothesized that herbimycin A would protect against intimal hyperplasia in the rat carotid balloon injury model.

Methods: Sprague-Dawley rats were randomized into four groups. A midline neck incision was made in the control group. In the remaining groups intimal damage was induced in the left

common carotid artery by balloon injury with a 2-Fr embolectomy catheter. Stress proteins were induced 18 h before carotid injury by hyperthermia (heat stress group) or pharmacologically with herbimycin A (herbimycin group). Two weeks after balloon injury animals were killed and their carotid intima:media area ratio (I:M ratio) was calculated by means of computerized planimetry.

Results: Heat stress and herbimycin significantly reduced the I:M ratio relative to the that in the balloon alone group.

Conclusion: Herbimycin A decreases neointimal hyperplasia in the rat carotid balloon injury model. Pharmacological inducers of HSPs may have a therapeutic role to play in preventing restenosis after endovascular procedures.

The immune response and blood transfusion in aortic surgery

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Background: Blood transfusion has been associated with immune modulation, tumour recurrence and postoperative infection. The role of inflammatory events at the time of operation was investigated in a randomized clinical trial comparing autologous and standard transfusion practice in elective aortic surgery.

Methods: Following local ethics committee approval, 128 patients were randomized prospectively to either acute normovolaemic haemodilution with cell salvage (autologous) or standard (homologous) transfusion. Total transfusion requirements were recorded on all patients throughout inpatient care. Venous blood was taken on six occasions: (1) before operation, (2) at wound closure, (3) 2 h, (4) day 1, (5) day 2 and (6) day 7 after operation. Samples were assayed for C-reactive protein, neutrophil elastase and the proinflammatory cytokines, tumour necrosis factor (TNF) α and interleukin (IL) 6.

Results: The rise in median (interquartile range) neutrophil elastase concentration during operation was significant for both groups but was 7.0 (–3.4–35.2) ng ml^{–1} in homologous patients compared with 1.8 (–9.3–10.5) ng ml^{–1} for autologous transfusion ($P < 0.05$). This increase was significantly higher in patients receiving homologous blood compared with controls at 34.0 ng ml^{–1} on wound closure ($P < 0.001$) and sustained to 7 days ($P < 0.05$). IL-6 peaked in the first 24 h after operation

	Mean(s.d.) I:M ratio
Control (n=8)	No measurable intima
Balloon injury (n=9)	1.84(0.61)
Balloon injury + heat stress (n=10)	1.14(0.52)*
Balloon injury + herbimycin (n=6)	0.86(0.47)*

* $P < 0.05$ versus balloon injury (analysis of variance with Tukey–Kramer post hoc test)

and TNF- α increased by 0.8 ng ml⁻¹ at 2 h in the homologous group only ($P < 0.05$). Patients receiving stored blood during operation showed a significantly greater rise in both TNF- α and IL-6 at 1.4 and 8.8 ng ml⁻¹ respectively at wound closure compared with -0.16 and 5.2 ng ml⁻¹ in those not requiring transfusion ($P < 0.05$).

Conclusion: Inflammatory mediators were generated during aortic surgery but were exacerbated by homologous transfusion. A multicentre trial would be required to determine whether these immunological changes translate into clinical consequences such as postoperative infection.

Angiogenic response to injury is preserved in the elderly

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Background: Multiply injured patients have raised levels of circulating vascular endothelial growth factor (VEGF). Angiogenic mechanisms in tissue repair appear to be attenuated in elderly animals. Fracture haematoma (FH) induces ectopic bone formation and its removal delays fracture healing. A prospective study was carried out to determine (1) the angiogenic potential of FH and (2) the effect of patient age on the angiogenic response to skeletal injury.

Methods: Sixteen patients under 40 years old and 16 patients aged over 75 years undergoing operation for isolated fractures were studied. Serum and FH were assayed for VEGF using an enzyme-linked immunosorbent assay. Endothelial cells were treated with supernatant from these samples and proliferation and tube formation determined using 5-bromo-2-deoxyuridine labelling and Rapi-Diff staining on Matrigel respectively. FH in a Matrigel vehicle was placed beneath a dorsal wound pocket in C57 mice, at 3 weeks the gel was removed, fixed, sectioned and immunostained for CD34, and the number of new vessels counted. Values are mean (s.e.m.) ($n = 16$ per age group). Analysis of variance was used for statistical analysis; $P < 0.05$ was considered significant.

Results: Control circulating VEGF concentration was lower in the elderly than in those aged under 40 years (31.4(4.7) *versus* 68.5 pg ml⁻¹). Compared with controls the response to fracture was enhanced tenfold in the elderly (305(71) pg ml⁻¹) compared with a fivefold increase in those under 40 years of age (315(61) pg ml⁻¹) (both $P < 0.05$ *versus* control). FH contained significantly more VEGF than serum, with no age-related difference (FH VEGF concentration 4367(1033) pg ml⁻¹ in patients under 40 years and 4569(1276) pg ml⁻¹ in those over 75 years; both $P < 0.05$ *versus* control). Serum from all injured patients induced angiogenesis *in vitro* as measured by endothelial cell proliferation (percentage of control) (control 100(12) per cent, patients aged less than 40 years 148(16) per cent, those over 75 years 143(11) per cent; $P < 0.05$ *versus* control) and by tubule formation (tubes per gel) (control 194(18), patients less 40 years 312(21), those over 75 years 299(24) tubes per gel; both $P < 0.05$ *versus* control). *In vivo* FH significantly enhanced tubule formation (tubes per gel) (control 68(9), patients under 40 years

207(21), those over 75 years 194(17) tubes per gel; $P < 0.05$ *versus* control).

Conclusion: All patients with skeletal injury, irrespective of age, have raised circulating VEGF levels. Their serum enhances angiogenesis *in vitro* and their FH is angiogenic *in vivo*. These findings demonstrate that skeletal injury induces a state of proangiogenesis and that human FH is inherently angiogenic. The biological activity of VEGF is not attenuated with advancing age. After skeletal injury both local and systemic VEGF-mediated angiogenic responses are preserved in the elderly.

Hypertonic saline dextran *versus* permissive hypotension for resuscitation of uncontrolled haemorrhage

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Background: While an artificial haemoglobin substitute remains elusive, fluid resuscitation of the trauma patient is still a subject for debate, especially where there is delay in reaching definitive medical care. The use of small-volume resuscitation in prehospital care has stimulated considerable interest, but there are few data on the effect of repeat administrations to the trauma patient. This study aimed to compare repeat dosing with 7.5 per cent sodium chloride plus 6 per cent dextran 70 (HSD) with permissive hypotension in an animal model of uncontrolled haemorrhage.

Methods: Nineteen instrumented, terminally anaesthetized, female pigs (weight 39–70 kg) were divided into three groups following an uncontrolled haemorrhagic insult sustained by causing intra-abdominal common iliac arterial bleeding. Group 1 animals ($n = 8$) were controls and received no treatment. Group 2 ($n = 5$) received HSD 4 ml kg⁻¹ at 1 and 4 h after the insult. Group 3 ($n = 6$) received HSD 4 ml kg⁻¹ at 1 and 7 h following the insult. Physiological, haematological and biochemical parameters were measured up to 12 h after insult, depending on survival. All studies were authorized under the Animals (Scientific Procedures) Act 1986.

Results: The initial insult produced a mean fall in blood pressure (BP) of 41 (range 28–63) per cent and in cardiac output (CO) of 44 (19–86) per cent. Following HSD infusion BP and CO rose in the treated groups to supranormal levels. Plasma sodium concentration increased significantly in groups 2 and 3 (mean rise 12 and 9 mmol l⁻¹ respectively; $P = 0.0001$, Mann-Whitney *U* test). A significant diuresis postinfusion was seen in groups 2 and 3, with mean urine output values of 128 and 154 ml h⁻¹ compared with 56 ml h⁻¹ in group 1 ($P = 0.0007$, $P = 0.0004$ respectively, Mann-Whitney *U* test). Overall survival analysis (log rank test) showed no difference between the three groups.

Conclusion: In this model of uncontrolled haemorrhage the use of HSD failed to improve survival compared with permissive hypotension, where a delay may occur in reaching definitive medical care. Instead, HSD appeared to accentuate

the metabolic derangement following trauma by significantly raising plasma sodium concentrations and causing a marked diuresis.

Serum vascular endothelial growth factor and soluble TIE-2 receptor as independent predictors of outcome in patients with colorectal cancer

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Background: A delicate balance exists between proangiogenic factors and antiangiogenic factors to regulate the process of angiogenesis. Vascular endothelial growth factor (VEGF) and angiopoietin are key regulators of angiogenesis with their soluble receptors, FLT-1 and TIE-2 respectively, acting as either negative inhibitors or stabilizers of ligand activities. Tumour necrosis factor (TNF) α may mediate apoptosis and necrosis of cancer cells as well as enhance angiogenesis through the induction of VEGF. Interleukin (IL) 12 has antiangiogenic properties, while IL-10 is its most potent inhibitor. This study aimed to investigate the relationship of VEGF with other angiogenic factors and to determine their clinical usefulness.

Methods: Venous blood was obtained from 47 patients with colorectal cancer (CRC) before curative resection. Serum levels of VEGF, soluble FLT-1 receptor (sFLT-1R), sTIE-2R, TNF- α and IL-10 were measured concurrently with quantitative enzyme-linked immunosorbent assay. Peripheral blood mononuclear cells were incubated with *Staphylococcus aureus* Cowan strain 1 *in vitro* for 24 h to assess IL-12 expression after stimulation. Median follow-up was 29 (20–35) months.

Results: Serum TNF- α activity was positive in 17 per cent of patients with CRC. The detection of serum TNF- α accurately predicted the development of metastases ($P=0.005$). Serum VEGF concentration was significantly higher in patients who developed metastases than in those who did not (median 708 versus 314 pg ml⁻¹; $P=0.002$). Serum sTIE-2R was significantly higher in patients who subsequently developed metastases than those who did not (median 58.5 versus 51.5 ng ml⁻¹; $P=0.03$). Serum sFLT-1R was detectable in only 74 per cent of patients with CRC. TNF- α activity correlated significantly with serum VEGF ($P=0.0002$), IL-10 ($P=0.01$), sFLT-1R ($P=0.005$) and sTIE-2R ($P=0.004$ levels). IL-12 correlated only with IL-10 level ($P=0.02$). The development of metastases was significantly correlated with the TNF- α activity ($P=0.002$), sTIE-2R ($P=0.03$) and VEGF ($P=0.001$). Using multivariate logistic regression analysis, the only independent predictors of outcome were sTIE-2R ($P=0.03$) and VEGF ($P=0.005$).

Conclusion: sTIE-2R and VEGF may play a role as two independent mediators of angiogenesis in the development of metastases, with VEGF being the most powerful predictor of outcome. These data also suggest that measurement of serum sTIE-2R may improve the predictive value of preoperative serum VEGF.

5-Aminosalicylic acid attenuates neutrophil-mediated ischaemia-reperfusion-induced acute lung injury

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Background: The therapeutic benefit of 5-aminosalicylic acid (5-ASA) in inflammatory bowel disease is established. It acts directly on the inflamed mucosa. The effect of 5-ASA in systemic inflammatory response is unknown. In this study, the role of systemic 5-ASA in preventing ischaemia-reperfusion-induced lung injury (IRI) was investigated in an experimental rat model.

Methods: Adult Sprague-Dawley rats ($n=7$ per group) were randomized to three groups: controls, IRI, and IRI pretreated with intravenous 5-ASA 430 $\mu\text{g kg}^{-1}$. Preliminary dose-response experiments indicated this to be the optimal therapeutic dose. Pulmonary microvascular permeability was assessed by measuring the concentration of bronchoalveolar lavage (BAL) protein. Pulmonary neutrophil infiltration was evaluated by measuring myeloperoxidase (MPO) activity and BAL neutrophil concentration. Lung histology was also examined.

Results:

	Control	IRI	IRI + 5-ASA
MPO (units g ⁻¹ min ⁻¹)	144.2(9.9)	210.4(10.6)*	165.8(8.6)†
BAL protein ($\mu\text{g ml}^{-1}$)§	191.2(22.8)	585.3(96.0)*	255.5(21.1)‡
BAL neutrophils (cells ml ⁻¹)	134.6(18.3)	928.2(57.1)*	272.4(43.0)‡

Values are mean(s.e.m.). * $P<0.01$ versus control, † $P<0.05$, ‡ $P<0.01$ versus IRI (analysis of variance with *post hoc* Scheffé test). §Log transformed for non-parametric data

Pretreatment with 5-ASA significantly reduced pulmonary vascular leak with decreased BAL protein concentration and histological evidence of diminished pulmonary congestion. These changes were associated with decreased neutrophil sequestration, as evidenced by decreased MPO and BAL neutrophil count.

Conclusion: This study demonstrates for the first time *in vivo* that systemic administration of 5-ASA attenuates ischaemia-reperfusion-induced tissue injury. Further toxicity studies are necessary for a potential new application of this drug.

Gastric mucosal pH predicts outcome in elective colonic surgery

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Background: Gastric mucosal pH (pH_i) has been correlated with outcome in critically ill patients but its predictive value in high-risk patients undergoing elective colonic surgery is unknown.

	Basal measurement		30 min ischaemia	
	Control	EIPA	Control	EIPA
Cellular pH	7.2(0.06)	6.9(0.08)*	6.5(0.09)‡	6.8(0.06)†
[Ca ²⁺] _i (nmol l ⁻¹)	138(27)	106(19)*	983(91)‡	262(26)†
Morphology (% normal)	> 95	> 95	< 30‡	> 70†
Barrier function (ohm cm ⁻²)	151(18)	147(21)	54(10)‡	113(17)†

* $P < 0.05$, † $P < 0.01$ versus controls; ‡ $P < 0.05$ versus basal values

Methods: Twenty high-risk patients (predominantly American Society of Anesthesiologists (ASA) grade III) undergoing major colonic resection were recruited into the study. In addition to standard monitoring, pH_i was recorded with a nasogastric tonometer (Tonometrics) after induction of anaesthesia, at completion of operation and at 4 and 24 h after operation. The patients were all admitted to a high-dependency unit for immediate postoperative care and any complications over a 30-day period were recorded. Patients were classified into group 1 (14 patients) with pH_i greater than 7.32 and group 2 (six patients) with pH_i less than 7.32 at 24 h.

Results: Group 1 patients had no complications. In Group 2 there were two deaths and four serious complications, comprising two wound infections, one prolonged ileus and a case of intraperitoneal sepsis from an anastomotic dehiscence. The median (interquartile range) pH_i at induction was the same for both groups, but by 24 h the pH_i was significantly different at 7.36 (0.07) in group 1 and 7.18 (0.08) in group 2 ($P < 0.001$, Wilcoxon test). Of all the parameters measured, only pH_i at 24 h had 100 per cent sensitivity and specificity (confidence interval 54–100 per cent) for the prediction of adverse outcome. Preoperative ASA grading and perioperative measurement of cardiorespiratory and renal function were of no value in predicting outcome.

Conclusion: A gastric pH_i value of less than 7.32 at 24 h following elective colonic surgery accurately predicts an adverse outcome.

Cellular acidification protects intestinal barrier function under ischaemic conditions

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Background: Loss of intestinal barrier function during mucosal ischaemia leads to bacterial translocation and endotoxaemia. Levels of cellular calcium ([Ca²⁺]_i) rise when energy stores are depleted during ischaemia. This activates degradative enzymes and leads to cellular autolysis. The hypothesis that preacidification paradoxically ameliorates tissue viability was examined.

Methods: Normal mucosa from colectomy specimens was mounted in oxygenated Ussing chambers. Barrier integrity

was assessed by recording transepithelial resistance (Ω cm²). Cellular pH and [Ca²⁺]_i of isolated crypts were monitored continuously by bis(carboxyethyl)carboxyfluorescein (BCECF) and Fura-2 spectrofluorescence imaging. Metabolic ischaemia was induced by inhibiting glycolysis and oxidative phosphorylation with 2-deoxyglucose (a non-hydrolysable substrate) and oligomycin A respectively. Cells were acidified with the sodium-hydrogen exchange inhibitor, ethylisopropylamiloride (EIPA) 10 μ mol l⁻¹. Values are given as mean(s.e.m.). The Mann-Whitney *U* test was used for statistical analysis ($n = 6$). **Results:** Ischaemia acidified crypts, increased [Ca²⁺]_i, induced membrane disruption and resulted in a 74 per cent loss of barrier integrity by 30 min. EIPA acidified crypts but reduced [Ca²⁺]_i changes and augmented barrier function during ischaemia.

Conclusion: The cellular consequences of ischaemia are the acidification and toxic [Ca²⁺]_i increases that accompany membrane disruption and loss of intercellular barriers. Although it also acidifies the cell, EIPA maintains cellular viability by quenching [Ca²⁺]_i increases. This finding indicates that there is a rapid-onset, reversible intervention to protect intestinal barrier function in patients with impaired splanchnic perfusion.

Interaction of haem oxygenase 1 and atrial natriuretic peptide in myocardial cytoprotection during surgery

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Background: All surgery results in cell damage, the extent of which is limited by both the severity of the insult and the host's response to it. Any mechanism that encourages cytoprotection can potentially reduce the amount of cell damage. Haem oxygenase (HO) 1 and atrial natriuretic peptide (ANP) have both been shown to be cytoprotective. During surgery cardiomyocyte expression is both induced and inhibited respectively. This study examined whether such an apparent paradox forms part of a feedback mechanism between HO-1 and ANP production.

Methods: Atrial tissue harvested from male Sprague-Dawley rats was flushed and incubated in oxygenated Krebs-Henseleit buffer at 37°C. Each pair of atria was randomly subjected to 5 h incubation with either hemin (an HO-1 inducer) 50 μ mol l⁻¹ or

hemin 50 $\mu\text{mol l}^{-1}$ and tin-protoporphyrin IX (an inhibitor of HO-1) 10 $\mu\text{mol l}^{-1}$. Differential reverse transcription-polymerase chain reaction (using α -actin as an internal standard) was employed to detect and semiquantify the amount of ANP and HO-1 messenger RNA present in 1 μg of extracted total RNA from each animal.

Results:

	ANP: α -actin	HO-1 α -actin
Control	13.7(1.2)	0.6(0.04)
Hemin	5.6(1.0)*	1.2(0.09)†
Hemin + tin-protoporphyrin	12.4(1.4)	0.8(0.08)

Values are mean(s.e.m.) for each group ($n = 5$ or 6). * $P < 0.002$, † $P < 0.002$ versus control (unpaired t test)

Conclusion: These results suggest that HO-1 inhibits ANP expression independent of a change in atrial stretch. This mechanism outlines for the first time the interaction between a cellular-based 'stress' protein and a cardiac hormone, both integral in preventing myocardial cell injury.

Endothelial selectin blockade moderates local skeletal muscle and remote organ reperfusion injury

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Background: A central role for the neutrophil in mediating the local and remote events of reperfusion injury following tissue ischaemia has been documented in a number of organs including skeletal muscle. Neutrophil adhesion to the micro-vascular endothelium is thought to be a prerequisite in the sequence of events leading to neutrophil activation and injury. This study examined the effects of endothelial selectin blockade with recombinant soluble P-selectin glycoprotein ligand-immunoglobulin fusion protein (rPSGL-Ig), a P- and E-selectin antagonist, in moderating both local and remote organ injury following lower torso ischaemia-reperfusion. The role of neutrophils was investigated by immunodepletion.

Methods: B10.D2/nSnJ mice were subjected to 2 h of bilateral hind limb ischaemia and 3 h of reperfusion. Extravasation of ^{125}I -labelled albumin, injected before reperfusion, was used to assess the hind limb and lung vascular permeability index (PI). Liver injury was assessed by determining serum alanine aminotransferase (ALAT) levels. Remote organ neutrophil sequestration was assayed by myeloperoxidase activity (MPO). Animals were maintained in accordance with National Research Council guidelines.

Results: Results are presented as mean(s.e.m.) with sham values subtracted. Hind limb PI in neutrophil-depleted animals ($n = 18$) was 1.3(0.07), a 38 per cent reduction compared with neutrophil-replete mice ($n = 29$), in which the PI was 2.0(0.1) ($P < 0.05$). A similar reduction in PI of 1.3(0.1) was observed in mice treated with rPSGL-Ig 1 mg kg^{-1} ($n = 8$; $P < 0.05$). Remote

organ injury was equally moderated in neutrophil-depleted and rPSGL-Ig-treated mice and was associated with reduced MPO activity, as indicated in the Table.

	Lung PI ($\times 10^{-3}$)	Lung MPO (units g^{-1})	ALAT (units l^{-1})	Liver MPO (units g^{-1})
Neutrophil depleted	0.3(0.5)*	77(8)*		
rPSGL-Ig	0.2(0.3)*	25(5)*	86(5)*	0.3(0.05)*
Neutrophil replete	4.9(0.6)	50(5)	132(6)	0.6(0.05)

* $P < 0.05$ versus neutrophil replete

Conclusion: Endothelial selectin blockade is as effective as neutrophil depletion in moderating local and remote organ injury following lower torso ischaemia-reperfusion.

Effects of leptin on human hepatocyte C-reactive protein production

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Background: Cachexia is a syndrome characterized by severe weight loss, mainly as a result of loss of muscle and fat. The syndrome is associated with activation of hepatic acute-phase protein (APP) synthesis. Recently leptin has been shown to play a role in body-weight regulation in various pathophysiological conditions. Leptin might therefore play a role in the activation of hepatic APP synthesis. This study examined the effect of leptin on human hepatocyte APP synthesis, especially C-reactive protein (CRP), which is a sensitive marker of the acute-phase response.

Methods: Human hepatocytes were isolated from wedge specimens of livers. Specimens were obtained from patients without an acute-phase response undergoing resectional surgery for colorectal cancer metastases. Specimens were flushed with heparinized saline and then perfused with collagenase. Repeated washings and Percoll gradient separation ensured a homogeneous population of hepatocytes with 95 per cent viability. Hepatocytes were plated on collagen-coated plates at 37°C. After 24 h, leptin in concentrations of 0.1, 1.0 and 10 ng ml^{-1} was added. The cells were incubated for a further 24 h before removal of the supernatants for analysis. A sandwich enzyme-linked immunosorbent assay was used to

	CRP ($\mu\text{g l}^{-1}$)
Control	70.2(11.6)
Leptin (ng ml^{-1})	
0.1	191.4(42.0)*
1.0	244.3(106.8)*
10	187.1(38.7)*

Values are mean(s.e.m.). * $P < 0.05$ versus control (Mann-Whitney U test)

determine levels of CRP. Appropriate controls were run in parallel. Experiments were repeated on three occasions.

Results: CRP levels were detectable in all hepatocyte cultures. The lower limit of detection was $0.07 \mu\text{g l}^{-1}$.

Conclusion: These data suggest that there is a direct effect of leptin on CRP production by human hepatocytes. The effect of leptin on the production of other acute-phase proteins remains to be determined and is the subject of current studies.

Fatty acid synthase signalling upregulates cytokine production after injury

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Background: Severe injury primes CD8+ T cells for an enhanced and fatal proinflammatory cytokine response to bacterial antigens. This response happens within 2 h of injury and suggests that there is a programmed response to the injury. The fatty acid synthase (Fas) CD95 pathway has previously been shown to induce cell death by apoptosis and also to activate a number of intracellular pathways leading to cytokine induction. This study aimed to determine whether Fas could play a role in the cytokine response to injury by examining the effects of injury on Fas-deficient mice.

Methods: Wild-type C57BL/6 (WT) and Fas-deficient C57BL/6-*lpr* (*lpr*) mice were scald burn injured and given $50 \mu\text{g}$ staphylococcal enterotoxin B (SEB). Deaths after 48 h were observed. Splenocytes were harvested 2 h after injury from WT and *lpr* mice and stimulated with SEB 200 ng ml^{-1} . Supernatants were harvested at 48 h for cytokine enzyme-linked immunosorbent assay (ELISA). Groups of all cells, groups of CD4+ T cell-enriched cells and groups of CD8+ T cell-enriched cells were created from 2 h sham or burn-injured spleens using a negative selection technique. These cells were stimulated with SEB 200 ng ml^{-1} for 48 h and ELISA was performed on the supernatants.

Results: Survival following SEB and injury was significantly better in *lpr* mice than in WT mice (100 versus 17 per cent;

$P < 0.01$). Injured *lpr* mice produced significantly less tumour necrosis factor (TNF) α and interferon (IFN) γ than sham *lpr* and both WT mice groups ($P < 0.01$). Injury upregulated the CD8+ T-cell production of IFN- γ and TNF- α in WT mice. This upregulation did not occur in *lpr* mice.

Conclusion: These findings support the hypothesis that Fas/Fas ligand can influence T-cell function early after injury. Fas/Fas ligand may provide an early signal to upregulate T-cell function after injury.

Hypoxia regulates the dynamic interplay between angiogenesis and bone formation

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Background: Endothelial cells (ECs) are implicated as osteo-progenitor cells and may produce osteogenic mitogens, such as endothelin (ET) 1 and insulin-like growth factor (IGF) 1. Hypoxia regulates endochondral ossification and fracture vascularization during fracture healing. This study examined the hypothesis that osteoblastic activity is regulated by ECs and that such regulation is modulated by hypoxia.

Methods: ECs from umbilical vein were incubated in hypoxic (2 per cent oxygen) and normoxic (21 per cent oxygen) conditions for 6, 12 and 24 h. Proliferation and viability were determined with a modified methyl tetrazolium (MTT) assay and tetrazolium bioreduction respectively. Production of ET-1 and IGF-1 was measured by enzyme-linked immunosorbent assay. Osteoblasts release vascular endothelial growth factor (VEGF), a potent endothelial cell mitogen, under hypoxic conditions. To clarify the cellular interaction between the two cell types, ECs were treated with supernatant from hypoxic osteoblasts for 24 h, and the same parameters as above were determined. Each experiment was carried out in triplicate ($n = 4$).

Results: Pretreating osteoblast supernatant with neutralizing monoclonal antibody to VEGF ($0.03 \mu\text{g ml}^{-1}$) before incubation of ECs reduced ET-1 and IGF-1 concentrations to control

	Normoxic conditions			Hypoxic conditions		
	6 h	12 h	24 h	6 h	12 h	24 h
EC ET-1 (pg ml^{-1})	213(38)	328(7)*	382(5)*	267(45)	443(42)*†	579(71)*†
EC IGF-1 (pg ml^{-1})	9 7(2.3)	14(1.6)	22(2)*	10(1)	22(3.6)*†	56(10)*†
Proliferation (%)	105(7)	112(10)	98(11)	120(5)†	148(4)*†	171(10)*†
Hypoxic osteoblast supernatant conditions						
EC ET-1 (pg ml^{-1})	1116(274)	1195(261)	1445(180)	1113(270)	1244(233)	1516(312)
EC IGF-1 (pg ml^{-1})	87.3(2.3)	97(4.5)*	107(1.2)*	135(4)†	168(1)*†	173(5)*†
Proliferation (%)	78(3)	86(3)*	90.5(2)*	92(2)†	96.5(2)*†	105(2.5)*†

Values are mean(s.e.m.). * $P < 0.05$ versus 6 h, † $P < 0.05$ versus normoxic condition (analysis of variance)

levels (ET-1 384(13) pg ml⁻¹, IGF-1 27(2) pg ml⁻¹), confirming that the angiogenic potential of hypoxic osteoblasts is due predominantly to VEGF.

Conclusion: Hypoxia induces EC proliferation and ET-1 and IGF-1 release in a time-dependent manner. In hypoxic conditions osteoblasts release VEGF, which significantly enhances EC proliferation and osteogenic mitogen release. In conditions of a healing fracture, hypoxia regulates the paracrine feedback between angiogenesis and bone formation.

Thermal preconditioning attenuates leucocyte-endothelium interactions in the microvasculature

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Background: The early event in endotoxin-induced tissue injury is adhesion and migration of leucocytes through the endothelium. This is a three-stage process: initially low-grade selectin-mediated adhesion (seen as a decrease in rolling velocity), followed by integrin-mediated adhesion and then transmigration. The aim of this study was to investigate the effect of thermal preconditioning (TC) on this process.

Methods: Intravital videomicroscopy was used to examine haemodynamic parameters, leucocyte rolling, adhesion and migration in rat mesenteric postcapillary venules. Sprague-Dawley rats were randomized into saline, lipopolysaccharide (LPS) and thermotolerance plus LPS groups. Thermotolerance was induced 48 h before administration of LPS by raising core body temperature to 41 ± 0.5°C for 15 min. LPS (055:B5 15 mg kg⁻¹) was administered via the jugular vein after baseline recording. Leucocyte rolling velocity (RV), the number of adherent and the number of migrated leucocytes were measured by intravital microscopy at baseline (0 min), 2, 10, 30, 60 and 90 min after LPS administration. Heat shock protein 72 (HSP72) expression in the tissues was determined by Western immunoblotting.

Results:

	Saline	LPS	TC + LPS
RV (µm s ⁻¹)	49.3(2.0)	38.0(2.5)*	41.3(2.4)
No. adherent (per 100 µm)	1.8(0.6)	10.0(1.6)††	4.0(0.7)
No. migrated (per field)	2.7(0.4)	8.3(1.6)††	3.0(0.7)

Values are mean(s.e.m.) 90 min after LPS administration. **P* < 0.05, †*P* < 0.01 versus saline; ††*P* < 0.01 versus TC + LPS (analysis of variance with Scheffé post hoc correction)

LPS significantly increased leucocyte adhesion and migration at 30, 60 and 90 min and decreased leucocyte RV. Thermotolerance significantly reduced leucocyte adhesion and migration. Expression of HSP72 was induced in mesentery, gut and lung by thermotolerance.

Conclusion: This study indicates that thermotolerance attenuated LPS-induced microvascular injury by decreasing leucocyte endothelial adhesion and migration.

Full-length soluble P-selectin but not the truncated form moderates complement-dependent injury

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Background: Skeletal muscle reperfusion injury is mediated in part by immunoglobulin (Ig) M natural antibody and classical complement pathway activation. P-selectin is an adhesion molecule expressed on activated endothelial and platelet surfaces. Recently the authors have reported a novel property of soluble P-selectin (sP-selectin) whereby the short consensus repeats block *in vitro* classical complement (C) pathway activation by selective inhibition of C1q. It is now hypothesized that full-length 140-kDa sP-selectin moderates complement-dependent skeletal muscle local reperfusion injury.

Methods: Bilateral tourniquets were placed above the greater trochanter of pentobarbital anaesthetized C57BL/6 mice for 2 h, followed by 3 h of reperfusion. Extravasation of ¹²⁵I-labelled albumin, injected before reperfusion, was used to assess hind limb vascular permeability index (PI). Semiquantitative evaluation of C3 deposition colocalized with IgM and skeletal muscle injury score (0–3) were also performed. Animals were maintained in accordance with National Research Council guidelines. A supernatant rich in sP-selectin was obtained from human platelets activated with adenosine 5'-diphosphate (ADP), adrenaline and calcium ions. Over 90 per cent purified 140-kDa sP-selectin (psP-selectin) was extracted from its supernatant, as characterized by total protein assay, enzyme-linked immunosorbent assay and Western blot, using antibody-coated magnetic beads. Animals were treated with either psP-selectin 11 µg kg⁻¹ or the 80-kDa truncated form of sP-selectin (tsP-selectin) standard (sCD62P; R & D Systems, Minneapolis, Minnesota, USA) 5 min before reperfusion.

Results: Results are presented as mean(s.e.m.) with sham value subtracted. PI in mice treated with psP-selectin (*n* = 17) was 1.08(0.06), a 43 per cent reduction compared with untreated animals where the PI was 1.91(0.12) (*n* = 19; *P* < 0.05). This decrease was not observed after treatment with tsP-selectin, where the PI was 1.85(0.19) (*n* = 15). Immunohistochemistry demonstrated colocalization of C3 with IgM in untreated mice and animals treated with tsP-selectin, and the tissue injury score was 2.45(0.15) and 2.09(0.20) respectively. In mice treated with psP-selectin the C3 deposition was negligible and the muscle injury score of 1.00(0.25) was significantly lower (*P* < 0.05).

Conclusion: Full-length sP-selectin but not tsP-selectin moderates complement-dependent skeletal muscle reperfusion injury.

Activated human neutrophils release hepatocyte growth factor

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Background: Hepatocyte growth factor (HGF) or scatter factor is a pleiotropic cytokine that has potent angiogenic properties. The authors have previously demonstrated that polymorphonuclear neutrophils (PMNs) are directly angiogenic by releasing vascular endothelial growth factor (VEGF). It was hypothesized that the acute inflammatory response can stimulate PMNs to release HGF. This study aimed to examine the effects of inflammatory mediators on PMN HGF release and the effect of recombinant human HGF (rhHGF) on PMN adhesion receptor expression and PMN VEGF release.

Methods: In the first experiment PMNs were isolated from five healthy volunteers and stimulated with tumour necrosis factor (TNF) α , lipopolysaccharide (LPS), interleukin (IL) 8 and formyl methionyl-leucyl-phenylalanine (fMLP). Culture supernatants were assayed for HGF using enzyme-linked immunosorbent assay (ELISA). In the second experiment PMNs were lysed to measure total HGF release, and HGF expression in the PMNs was detected by Western immunoblotting. Finally, PMNs were stimulated with rhHGF. PMN CD11a, CD11b and CD18 receptor expression and VEGF release were measured by means of flow cytometry and ELISA respectively.

Results:

Incubation time	Stimulated PMNs			
	Control	TNF- α (5 ng ml ⁻¹)	LPS (10 ng ml ⁻¹)	fMLP (50 nmol l ⁻¹)
2 h	118.3(41.8)	755.3(216.4)*	484.5(221.0)*	565.2(278.4)*
6 h	221.5(92.0)	889.0(191.7)*	706.4(360.7)*	347.7(97.9)*

Values are mean(s.e.m.) PMN HGF release (pg ml⁻¹). * $P < 0.05$ (paired Student's *t* test)

TNF- α , LPS and fMLP stimulation resulted in significantly increased release of PMN HGF compared with controls. IL-8 had no effect. Total HGF release following cell lysis and

Western blotting suggests that HGF is released from intracellular stores. rhHGF did not alter PMN adhesion receptor expression and had no effect on PMN VEGF release.

Conclusion: This study demonstrates that proinflammatory mediators can stimulate HGF release from a PMN intracellular store and that activated PMNs, in addition to secreting VEGF, have further angiogenic potential by releasing HGF.

Interleukin 10 is not essential for survival or for modulating T-cell function after injury

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Background: Interleukin (IL) 10 is thought to be protective in injury and sepsis. It has been previously reported in a murine burn model that anti-IL-10 antibody prevents loss of T helper 1 (Th1) lymphocyte function and restores normal resistance to infection. This study aimed to define further the role of endogenous IL-10 following injury.

Methods: In three independent experiments, groups of five wild-type (WT) C57BL/6 mice or five IL-10 knockout (IL-10^{-/-}) C57BL/6 mice underwent burn or sham injury under anaesthesia in accordance with local ethics committee guidelines. Mice were immunized at the time of injury with a T-dependent antigen, trinitrophenol-haptenated chicken ovalbumin (TNP-OVA). At day 10 all surviving animals were killed and serum and spleen cells harvested. TNP-specific antibody isotype and the cytokines tumour necrosis factor (TNF) α , interferon (IFN) γ and IL-10 were assessed by immunoassay. Antigen-specific proliferation was assessed by determining tritiated thymidine incorporation.

Results: The 10-day survival rate of IL-10^{-/-} burn mice (80 per cent; $n = 15$) was equivalent to that of WT mice (73 per cent) despite significantly increased antigen-specific TNF- α production by IL-10^{-/-} spleen cells. As in WT mice, antigen-induced proliferation and IFN- γ production by IL-10^{-/-} burn splenocytes were diminished compared with values in sham splenocytes. IL-10^{-/-} burn mice failed to produce a Th1-dependent immunoglobulin G_{2a} response to TNP-OVA, whereas IL-10^{-/-} sham mice produced this antibody isotype at a titre comparable to that in WT sham mice.

	WT sham	WT burn	IL-10 ^{-/-} sham	IL-10 ^{-/-} burn
TNF- α (pg ml ⁻¹)	120(3.4)	212(42)*	503(58)	990(109)*
IFN- γ (units ml ⁻¹)	23(3.1)	5(1)*	850(110)	245(14)*
IL-10 (pg ml ⁻¹)	606(98)	512(29)	<75	<75
Proliferation (c.p.m.)	18 931(667)	14 233(747)*	34 661(414)	3 182(342)*

* $P < 0.05$ versus sham (analysis of variance with the Tukey-Kramer multiple comparisons test)

Conclusion: IL-10 may play a role in altering T-cell function after injury in intact animals, but is not essential for survival or for downregulating Th1 responses.

Prospective study of the value of acridine orange leucocyte cytospin in prolonging the lifespan of central venous catheters in patients with suspected catheter-related sepsis

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Background: Up to 85 per cent of central venous catheters (CVCs) removed on suspicion of catheter-related sepsis (CRS) are uninfected on subsequent culture. Acridine orange leucocyte cytospin (AOLC) is a highly sensitive and specific test for the rapid detection of CRS *in vivo*. This study aimed to evaluate the role of AOLC in prolonging the survival of CVCs with suspected CRS.

Methods: Between May 1998 and August 1999, 50 patients with suspected CRS were evaluated prospectively. Clinical suspicion of CRS occurred when the patient exhibited features of sepsis in the absence of an obvious source of infection. CRS was defined as the isolation of the same micro-organism from the peripheral blood and in significant numbers on the CVC in the presence of clinical sepsis. Blood samples were obtained from CVCs for AOLC test and culture on the day of suspicion of CRS, and from a peripheral venous site for quantitative surface-plate blood culture. CVCs that would otherwise have been removed were left *in situ* if the AOLC test was negative. All catheters were followed up and cultured upon removal. The intervals from insertion of the catheter to the time of suspicion of CRS and the time of catheter removal were compared by means of Kaplan–Meier survival analysis.

Results: The median interval between catheter insertion and suspicion of CRS was 11 (range 2–27) days. The catheter was removed on the day of suspicion of CRS in six patients (12 per cent) with a positive AOLC test, in which CRS was later confirmed. The AOLC test was negative in the remaining 44 patients (median 24 (range 4–180) days; $P < 0.0001$) and significantly prolonged the clinical usage of the catheters.

Conclusion: The AOLC test identifies non-infected catheters and allows a significant extension of their lifespan. This finding may have considerable clinical and economic implications.

Cytotoxic T cells in abdominal aortic aneurysm wall

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Background: Marked inflammatory infiltration within abdominal aortic aneurysms (AAAs) is associated with increased matrix metalloproteinase expression and subsequent extracel-

lular degradation. Previous investigators have identified cell-mediated immunity as an important factor in the pathogenesis of AAA. The aim of this study was to identify the inflammatory cells present in AAA tissue.

Methods: Immunohistochemistry using T-cell markers was carried out on 33 samples of formalin-fixed, paraffin-embedded aortic walls obtained at the time of elective AAA surgery. Sections were stained with haematoxylin and eosin, and with monoclonal antibodies to CD3, CD4 and CD8. Activated cytotoxic cells were detected with monoclonal antibodies to CD57, which is present on natural killer (NK) cells, and TIA-1, which is a membrane protein present in cytotoxic T lymphocytes and NK cells. Sections were scored on the medial infiltrate by a consultant haematologist, and the degree of staining was graded as absent, mild, moderate or strong.

Results: An inflammatory infiltrate was present in 31 of 33 patients and all infiltrates contained mature CD3+ T lymphocytes. CD4+ T lymphocytes were present in 26 of 33 AAA walls and 30 contained CD8+ T lymphocytes. The numbers of CD4+ and CD8+ T lymphocytes in each infiltrate were broadly similar. CD57+ NK cells were detected in 13 of 33 aneurysms, demonstrating mild infiltration only. In 30 of 33 AAA walls TIA-1 positive cells were present, which in 19 of 33 cases were moderate or strong infiltrates, indicating the presence of activated cells with cytotoxic potential.

Conclusion: These results demonstrate that cytotoxic molecules expressing T cells are frequently present in the media of AAAs and may therefore contribute to arterial wall injury and disease progression.

Smoking, cadmium accumulation and aortic aneurysm

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Background: Smoking is an important risk factor for abdominal aortic aneurysm (AAA), a disorder associated with loss of medial smooth muscle cells. Cadmium, one of the toxic components inhaled in cigarette smoke, is known to alter the metabolism of aortic smooth muscle cells. The hypothesis that excess cadmium accumulation in the abdominal aorta was associated with the development of aneurysms was investigated.

Methods: Samples of abdominal aorta were obtained at the time of operation from 12 patients with AAA (seven men and five women; mean age 72 years) and at autopsy from 17 patients (ten men and seven women; mean age 76 years) with undilated aorta (diameter 1.6–2.2 cm). The smoking history of all patients was noted. The aorta was dissected into three layers (intima, media and adventitia) and each was dried to constant weight, hydrolysed and cadmium measured by atomic absorption spectrometry. In separate experiments bromodeoxyuridine uptake and picogreen assay of DNA was used to investigate the effect of cadmium on the proliferation of cultured aortic smooth muscle cells.

Results: The mean(s.e.m.) cadmium content of the intima, media and adventitia was 1.14(0.24), 3.25(0.53) and 1.87(0.38) ng per mg dry weight respectively. The medial concentration was significantly higher than the concentration in the other two layers ($P < 0.005$). The medial cadmium content was similar in AAAs and in normal diameter aortas: 3.65(1.00) and 2.97(0.59) ng per mg dry weight respectively. Only trace amounts of cadmium were present in the aorta of those who had never smoked and there was a strong positive association between medial cadmium content and pack-year history of smoking ($r_s = 0.87$, $P < 0.001$). Cadmium inhibited the proliferation of smooth muscle cells cultured on polymeric collagen, bromodeoxyuridine uptake (IC_{50} 1.4 nmol l⁻¹) and DNA content (IC_{50} 6.3 nmol l⁻¹). Cadmium was less toxic, by more than tenfold, to smooth muscle cells cultured on fibronectin, monomeric collagen or plastic.

Conclusion: Cadmium accumulates selectively in the medial layer of the abdominal aorta of smokers, where it may inhibit DNA synthesis and proliferation of smooth muscle cells. The toxic effects of cadmium on cultured smooth muscle cells depend on their underlying matrix, and this may explain why the accumulation of cadmium in aortic media was not associated with the development of aneurysms.

Cell salvage in aortic surgery

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Background: Aortic surgery usually requires a blood cross-match of 4–6 units. A randomized clinical trial was undertaken to evaluate acute normovolaemic haemodilution (ANH) and intraoperative cell salvage (ICS) as alternatives.

Methods: With ethics committee approval, 128 patients undergoing elective aortic surgery were randomized prospectively to (1) autologous transfusion combining ANH with ICS and (2) homologous transfusion using standard transfusion practice. A transfusion trigger of haemoglobin 9 g dl⁻¹ in the absence of any pressing clinical need was used for all patients. Total transfusion requirements were recorded throughout inpatient care.

Results: Autologous transfusion did not influence stored blood requirements in the 34 patients with occlusive disease, in whom median blood loss was only 651 ml. In patients with abdominal aortic aneurysm (AAA), median blood loss was 1080 ml with homologous and 1000 ml with autologous transfusion (P not significant). Autologous transfusion reduced transfusion needs only when blood loss exceeded 1000 ml, when 33 per cent of patients having autologous transfusion required stored blood (mean 0.58 units) compared with 72 per cent of those having homologous transfusion (mean 2.92 units; $P < 0.01$). Larger blood losses (more than 1000 ml) were associated significantly with higher estimated blood volume (4946 *versus* 4594 ml; $P < 0.01$), longer operations (162 *versus* 127 min; $P < 0.01$) and lower platelet counts before operation (201.7 *versus*

238.2 $\times 10^9$ l⁻¹; $P < 0.01$). Blood loss was not related to preoperative haemoglobin level, type of graft, aneurysm size or aspirin intake.

Conclusion: ICS is useful in elective AAA repair only when estimated blood volume, preoperative platelet count and expected duration (technical difficulty) of the operation predict a blood loss exceeding 1000 ml.

Gut permeability increases after open but not endovascular aneurysm repair

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Background: Abnormal gut permeability following open aortic aneurysm repair (OAR) has been attributed to ischaemia–reperfusion injury due to aortic clamping.

Methods: Gut permeability was measured using lactulose–mannitol (L-M) on the morning before and the morning after both OAR and endovascular aneurysm repair (EVAR) in 16 patients undergoing elective infrarenal aneurysm repair (EVAR, nine; OAR, seven). Local ethics committee approval was obtained. EVAR comprised modular stent grafts inserted using bilateral common femoral arteriotomy under general anaesthesia.

Results: Mean (range) cross-clamp times were 47.7 (29–65) min for OAR compared with 65.3 (45–85) min for EVAR ($P < 0.05$). Blood loss was higher at 836 (229–1034) ml during OAR, compared with 267 (50–617) ml for EVAR ($P < 0.01$). Median (interquartile range) L-M permeability increased significantly following OAR, from 0.02 (0.009–0.02) before to 0.02 (0.01–0.1) after operation ($P < 0.05$, Wilcoxon test), but did not alter after EVAR at 0.01 (0.012–0.02) before to 0.02 (0.01–0.02) after operation. The perioperative increase in gut permeability correlated with blood loss during OAR but not during EVAR ($P < 0.05$, Spearman test).

Conclusion: Increased gut permeability following aortic surgery does not depend on ischaemia–reperfusion injury alone. It is possible that manipulation of the small bowel during open surgery or the severity of the surgical trauma itself plays a greater role.

Adenosine modulates mucosal barrier function during intestinal ischaemia

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Background: Bacterial translocation and endotoxaemia may occur during periods of mucosal ischaemia due to loss of intestinal barrier function. Multiple organ dysfunction syndrome may develop if the insult is severe or prolonged. The

effect of experimentally induced ischaemia on the mucosal barrier of human colon was examined *in vitro*.

Methods: Normal mucosa, microdissected from fresh colectomy specimens, was mounted in Ussing chambers and oxygenated in Ringer solution. 'Ischaemia' was induced by inhibiting glycolysis and oxidative phosphorylation with 2-deoxyglucose (a non-hydrolysable substrate) and oligomycin A respectively. Barrier integrity was assessed by recording transepithelial resistance (ohm cm^{-2}). Values were given as mean (s.e.m.) ($n=6$). Student's *t* test was used for statistical analysis. University ethics committee approval was granted.

Results: Controls exhibited stable transepithelial resistance ($146(13) \text{ ohm cm}^{-2}$), indicating 'normal' barrier function. Ischaemia produced a biphasic fall in resistance: an early transient trough (correlating with chloride secretion) ($64(9) \text{ ohm cm}^{-2}$) was followed by a progressive loss of barrier integrity (27 per cent at 40 min). Aspirated luminal bath fluid from ischaemic colon at 10 min induced a similarly transient secretion when added to controls. Secretion was inhibited by an adenosine receptor antagonist (8-phenyltheophylline) in both groups ($P<0.01$). Previous exposure of mucosa to adenosine ameliorated barrier function during subsequent ischaemia (65 per cent at 40 min; $P<0.01$).

Conclusion: Ischaemic colonic mucosa generates secretion through release of adenosine in an autocrine or paracrine manner. Meanwhile adenosine protects mucosal barrier function during periods of ischaemia. This finding indicates a defence mechanism to protect intestinal barrier integrity that provides a potential target in the management of patients with impaired splanchnic perfusion.

Systemic interleukin 6 response during aortic aneurysm repair is mediated via the portal circulation

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Background: Dramatic interleukin (IL) 6 responses have been seen after abdominal aortic aneurysm (AAA) repair, especially

in patients who subsequently suffer serious postoperative complications. This study aimed to determine whether the IL-6 response arises from limb ischaemia-reperfusion injury secondary to aortic cross-clamping, or alternatively from a colonic ischaemia-reperfusion injury.

Methods: Serum IL-6 concentration was measured in venous blood from seven patients undergoing elective AAA repair. Samples were taken during operation from (1) the superior vena cava (SVC), (2) the external iliac vein (EIV) and (3) the inferior mesenteric vein (IMV). Venous samples were taken from all three sites before, during and 20 min after aortic cross-clamping. The mean values were compared using one-way analysis of variance.

Results: There was no difference between the mean concentrations of IL-6 in the samples taken before aortic clamping from SVC, EIV and IMV (5.6, 5.6 and 4.5 pg ml^{-1} respectively). During clamping the concentrations of IL-6 increased in all three samples (8.7, 12.2 and 28.6 pg ml^{-1} respectively) with the highest rise observed in blood from the IMV, but the difference was not statistically significant. After clamp release the concentration of IL-6 in blood from the IMV (46.9 pg ml^{-1}) was significantly higher ($P=0.01$) than that in blood from the SVC or EIV (19.4 and 19.5 pg ml^{-1} respectively).

Conclusion: This study suggests that it is the colonic ischaemic injury, not the ischaemic lower limbs, that drives the IL-6 response in the early perioperative period in patients undergoing AAA repair.

Pilot study of pressure gradient-guided angioplasty

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Background: Quality control using translesional pressure gradients (PGs) may improve the outcome of percutaneous transluminal angioplasty (PTA) for claudication, rest pain or tissue loss.

Methods: PG-guided PTA was performed in 18 limbs; the translesional PG was corrected if possible to 10 mmHg or less,

	PG-guided PTA	Non-PG-guided PTA
Pre-PTA ABPI*	0.64 (0.37–0.99)	0.57 (0.32–1.00)
Post-PTA 24-h ABPI*	0.86 (0.42–1.00)	0.66 (0.42–1.00)
Change in 24-h ABPI*	0.15 (0.03–0.39)	0.13 (–0.11 to 0.38)
Limbs with increase in ABPI ≥ 0.15	11 of 18	9 of 16
Limb amputation following PTA failure	0	2
Death following PTA	0	2
Symptomatic success at 6 weeks		
For all limbs in each group	14 of 18	7 of 16†
For intermittent claudication	8 of 9	3 of 6
For rest pain or tissue loss	6 of 9	4 of 10
For femoropopliteal segment PTA	8 of 10	4 of 9
For iliac segment PTA	6 of 8	3 of 7

*Values are median (range). † $P=0.03$

either by PTA alone or by PTA with stenting. In a further 16 limbs the quality of the PTA was judged by conventional completion angiography alone. Patients undergoing PG-guided PTA had the mean intra-arterial pressure (MAP) recorded using a 7-Fr Multitrack angiographic catheter and a Logical pressure transducer (PG = MAP above lesion - MAP below lesion). All patients had the ankle:brachial pressure index (ABPI) measured before and 24 h after PTA. Haemodynamic success was defined as an increase of 0.15 or more in the 24-h ABPI. Symptomatic success was defined as the improvement of at least one grade according to Society of Vascular Surgery/International Society of Cardiovascular Surgery guidelines.

Results: The median (range) pre-PTA PG was 23 (3–85) mmHg and the median post-PTA PG was 2 (0–21) mmHg. The median percentage improvement in PG was 84 (50–100) per cent. Fourteen of 18 limbs in the PG-guided group achieved a post-PTA residual PG of less than 10 mmHg.

Conclusion: This pilot study suggests that PG-guided PTA improves the results of PTA, although a larger study with longer follow-up is required.

Potential mechanism of improved walking performance after upper body exercise training

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Background: Walking exercise training elicits symptomatic improvements in claudicants, although the mechanisms are poorly understood. Important factors include localized adaptations or systemic cardiovascular changes. This study used an upper body exercise training programme to separate localized and systemic effects and to evaluate the influence of cardiovascular fitness on walking distance in stable claudicants.

Methods: Patients were recruited and baseline cardiovascular fitness was established by means of arm ergometry in which the work rate (W) was increased every 3 min to the point of muscle fatigue. The relationship between power and heart rate during arm exercise was used as an indicator of cardiovascular fitness. Patients were randomized to a 6-week training programme involving two supervised sessions per week of upper body (arm crank) training ($n=24$) or no training (control, $n=15$). The maximum walking distance (MWD) was determined before and after training using the shuttle walk test, as was the maximum power generated during leg ergometry (MLP). All values are median.

Results: The heart rate response to increasing power was reduced after training, resulting in a decrease in the heart rate at the penultimate power level ($P<0.003$, Wilcoxon test). These changes reflect an improved cardiovascular fitness and were accompanied by increases in the MWD (290 versus 371 m; $P<0.001$, Wilcoxon test) and the MLP (75 versus 100 W; $P<0.001$, Wilcoxon test). There were no significant changes in the control group.

Power (W)	Heart rate (beats per min)			
	Arm training group		Control group	
	Pre-training	Post-training	Pre-training	Post-training
10	111	98	115	117
20	122	112	121	120
30	131	120	130	140
40	140	129	151	155
50	154	130	162	167

Conclusion: These findings indicate that cardiovascular fitness plays a pivotal role in exercise-induced symptomatic improvements in claudicants.

Smoking causes a dose-dependent increase in neutrophil L-selectin concentration

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Background: Cigarette smoking may cause atherosclerosis through endothelial injury, neutrophil activation and upregulation of adhesion molecules, which are thought to be shed from the surface of activated cells into the serum. The immediate effects of cigarette smoking on neutrophil-bound L-selectin and serum L- and E-selectin were examined in 12 smokers with claudication and in 12 healthy control smokers.

Methods: Venous blood was sampled before and at 5 and 10 min after smoking two cigarettes and then at 5, 10 and 30 min after a further two cigarettes. Surface bound L-selectin was expressed as mean fluorescence index (MFI; arbitrary units) using flow cytometry. Soluble L- and E-selectin were analysed in serum using an enzyme-linked immunosorbent assay. Local ethics committee approval was obtained.

Results: The mean (s.d.) neutrophil L-selectin concentration increased significantly from 3.43(0.67) MFI at baseline to 3.64(0.76) MFI 10 min after smoking two cigarettes, and increased still further 30 min following two more cigarettes, to 3.90(0.92) MFI ($P<0.001$). There was no difference between claudicants and controls. Before smoking, serum L-selectin concentration was significantly lower in claudicants at 687(106) ng ml⁻¹ compared with 814(137) ng ml⁻¹ in controls ($P<0.004$). Neither serum E- nor L-selectin concentration changed significantly after smoking four cigarettes.

Conclusion: Smoking caused a dose-dependent increase in neutrophil expression of L-selectin, which may be important as a cause of atherosclerosis or thrombosis. The lower L-selectin levels in claudicants, and the absence of a rise in serum adhesion molecules upon smoking, suggests that consumption may be part of a negative feedback mechanism.

Sex dependence of the association of infrainguinal graft failure with lipid metabolism

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Background: Lipoprotein lipase (LPL) plays a major role in the hydrolysis of triglyceride-rich lipoproteins. LPL gene variation has been associated with premature coronary artery disease but LPL activity has not been studied before in patients with peripheral vascular disease. This study compared endothelial LPL activity in patients with failed and successful infrainguinal bypass grafts.

Methods: Twenty-eight patients with occluded grafts were identified from a prospective database and matched with 20 controls with functioning grafts. Blood samples for analysis of endothelial LPL activity were taken before and 30 min after an intravenous bolus of heparin (50 units kg⁻¹). Samples were stored at -70°C and analysed in a single batch measuring the release of [³H]oleic acid from [³H]triolein.

Results: The preheparin LPL activity was effectively zero in all groups.

After heparin	LPL activity (mmol h ⁻¹ ml ⁻¹)
Patent graft	
Women (n=6)	79.7(22.6)
Men (n=12)	114.2(19.8)
Occluded graft	
Women (n=12)	82.5(18.5)
Men (n=14)	58.9(8.3)*

Values are mean(s.e.m.). *P ≤ 0.01 (Student's unpaired t test)

Conclusion: Heparin-releasable endothelial LPL activity is sex dependent and lower in men with failed infrainguinal bypass grafts. Identification and treatment of abnormal lipid metabolism may provide a method of improving the outcome of infrainguinal reconstruction.

Relationship of symptoms and repeated monitoring to spontaneous cerebral emboli in carotid stenosis

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Background: Spontaneous cerebral emboli (SCEs), detected by transcranial Doppler (TCD) monitoring over 1 h, have been associated with an increased risk of stroke in patients with carotid disease. Fifteen patients taking aspirin with symptomatic 70–99 per cent carotid stenosis were investigated to evaluate the duration of monitoring and reproducibility in individuals.

Methods: TCD insonation of the ipsilateral middle cerebral artery was performed over six 1-h sessions on different days. Suspected SCEs were recorded on digital audiotape and validated by a panel of three.

Results:

Hour	Cumulative no of patients with SCEs
1	1
2	2
3	4
4	6
5	9
6	9

The number of patients with SCEs increased with each hour of monitoring up to 5 h when nine (60 per cent (95 per cent confidence interval 35–85 per cent)) of 15 were positive. Only two patients had SCEs in more than 1 h and two others had bursts of SCEs in a single hour. The relationship between time since last cerebral symptom and SCEs was not significant whether measured as total emboli ($r_s = -0.26$), maximum SCEs in 1 h ($r_s = -0.32$) or the presence or absence of SCEs ($r_s = 0.37$). Patients with SCEs tended to more recent symptoms at a median of 2 months, compared with 9 months for those without ($P = 0.17$). Three patients with no symptoms over 12 months still had SCEs.

Conclusion: Several hours of monitoring are required to exclude SCEs and, as most patients will develop emboli over time, SCE monitoring is unlikely to be of value in patients with symptomatic severe carotid stenosis.

Relationship between cerebral blood flow and symptoms in severe carotid stenosis

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Background: Carotid disease may cause symptoms by hypoperfusion, emboli or both. The influence of carotid stenosis on cerebral blood flow was investigated and related to symptoms. **Methods:** Flow in the intracerebral internal carotid artery (ICA), middle cerebral artery (MCA) and basilar artery (BA) was measured by phase-contrast magnetic resonance imaging (1.5-Tesla Philips Gyroscan) in 69 patients with more than 70 per cent carotid stenosis. Symptoms were categorized as: (1) amaurosis fugax, (2) focal transient ischaemic attack (TIA), (3) 'global' TIA (dizziness, blackouts) and (4) stroke.

Results: Median (interquartile range) flow through the ipsilateral (more severely stenosed) ICA at 146 (55–246) ml min⁻¹ was lower than that in the contralateral ICA at 377 (285–496) ml min⁻¹ ($P < 0.01$, Mann-Whitney U test). Reduced flow in the ipsilateral ICA was associated with a fall in total ICA flow

($r_s = 0.44$, $P = 0.01$) and a rise in contralateral ICA flow ($r_s = -0.29$, $P = 0.019$). Ipsilateral MCA flow at 173 (136–198) ml min⁻¹ was similar to contralateral MCA flow at 165 (123–203) ml min⁻¹ (P not significant). In patients with global symptoms, MCA flow was significantly reduced on the ipsilateral side compared with the contralateral side ($P < 0.01$). In other symptom groups there was no reduction in total flow (sum of ICA or sum of MCA flows) or in flow in the MCA to the affected cerebral hemisphere.

Conclusion: The contralateral ICA compensates for ICA stenosis in most patients, and the circle of Willis redistributes flow to prevent MCA asymmetry except in patients suffering from global TIA. These less well defined symptoms deserve more attention.

Sulphasalazine at colon molar concentrations in inflammatory bowel disease is cytotoxic to colorectal cancer cells *in vitro*

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Background: Recent publications have suggested a reduced risk of development of colorectal adenocarcinoma in patients with inflammatory bowel disease treated with sulphasalazine compared either with those not treated (due to non-compliance or medical direction) or within the general population. The aim of this study was to evaluate the direct effect of equimolar concentrations of sulphasalazine on colorectal cell lines Colo 201 and Colo 205.

Methods: Colo 201 and Colo 205 cells cultured to confluence were trypsinized and resuspended at a concentration of 10^6 cells per ml in 10 per cent fetal calf serum in RPMI culture medium. Some 100 µl of the suspension was cultured with sulphasalazine 10 mmol l⁻¹ or control (ammonium hydroxide) for up to 24 h. At designated times the cells were labelled with propidium iodide (PI) for apoptosis. Resultant fluorescent activity was analysed in 10^4 cells on a forward scatter/propidium iodide dot plot in a flow cytometer.

Results: At sulphasalazine 10 mmol l⁻¹ the mean percentage of apoptotic and necrotic cells as detected by PI uptake was 99 and 92 per cent respectively for the two cell lines.

Conclusion: These findings suggest that sulphasalazine is directly cytotoxic to colorectal cancer cells *in vitro* and this

cytotoxicity may play a part in the reduced risk described in previous epidemiological studies. The findings also fit with the protective effects found with non-steroidal anti-inflammatory drugs in the general population. Would 5-aminosalicylic acid have the same effect? Studies are required on the possible role of sulphasalazine as an adjunctive therapy for colorectal cancer.

Reducing delays and emergencies in patients with colorectal cancer

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Background: Despite numerous studies spanning three decades, the link between delays in the diagnosis and treatment of patients with colorectal cancer (CRC) and outcome, in terms of stage and mortality, remain contradictory. Little attention has been paid to early observations that delays may be disadvantageous in patients in whom emergency surgery becomes necessary. Almost one-third of patients with CRC are treated as emergencies, accounting for about half the total mortality burden. Given that there are no established strategies for reducing emergency rates in patients with CRC, this study investigated the link between delays and emergency treatment.

Methods: Prospective data collection from seven hospitals in Greater Birmingham was undertaken from 1 April 1996 to 31 March 1997 as part of the Confidential Interactive Multidisciplinary Audit of Colorectal Cancer project. Six hundred patients were surveyed. Questionnaires were completed by clinicians and quality control was performed by random review of clinical records. Data were collected on the proportion of elective patients undergoing emergency treatment and on the outcome of these 'crossover' patients. The effects of a fast-track system of CRC care on delays and crossover to emergency treatment was studied.

Results: General practitioners had an index referral rate of only 19 per cent to accident and emergency departments, yet hospitals treated 30 per cent of CRC cases as emergencies. Patient flow analysis ($n = 434$) showed that one-half of the emergency cases (53 of 107) were initially referred through the elective route, which was characterized by long delays. The median time from referral to treatment for elective cases was 9 weeks, with 38 per cent of patients waiting longer than 3 months. The emergency cohort had a higher mortality rate (17 *versus* 7 per cent), more general complications (24 *versus* 13 per cent) and longer hospital stay (median 18 *versus* 14 days) than elective cases. Subgroup comparison of index emergency patients and crossover emergency patients showed no difference in mortality rate (15 *versus* 17 per cent), surgical complication rate (15 *versus* 12 per cent), general complication rate (19 *versus* 16 per cent) and median postoperative stay (12 days). Results from one centre showed that the time between referral and operation can be reduced by fast-track, team-based models of care. Median time from outpatients to

	PI uptake (%)					
	1h	2h	4h	8h	12h	24h
Colo 205						
Control	24	41	33	20	14	39
Sulphasalazine	57	94	95	99.8	99.8	99.9
Colo 201						
Control	21	15	33	16	16	9
Sulphasalazine	99	99	95	99	100	100

operation was reduced from 24 to 18 days. For patients with rectal cancer (inclusive of preoperative radiotherapy) the reduction was from 24 to 18 days, and for those with colonic cancer from 25 to 13 days.

Conclusion: These results suggest that delays in the elective process of care can lead a considerable number of patients to crossover to the emergency setting. These crossover patients have a poorer outcome. Time from referral to surgery can be reduced substantially through team-based fast-track services. Shortening the time to treatment may be expected to reduce the number of crossover emergency cases. Such an initiative may have a greater impact on survival rates than current adjuvant therapies in patients with this common cancer.

Relationship between growth inhibition and cyclo-oxygenase 2 gene expression induced by aspirin and NS398 in colonic cancer

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Background: Aspirin is associated with a reduced risk of death from colorectal cancer. The exact mechanism of action and the role of cyclo-oxygenase 2 (COX-2) need to be delineated. This study aimed to determine the effect of aspirin and the selective COX-2 inhibitor NS398 on (1) *in vitro* growth and (2) COX-2 gene expression levels of human colonic tumour cell lines.

Methods: For *in vitro* growth, the test compounds were prepared in tissue culture medium at a concentration range of 10–10 000 $\mu\text{mol l}^{-1}$. Proliferation was assessed by the methyl tetrazolium assay. To estimate COX-2 gene expression, total RNA was extracted from cell pellets following *in vitro* treatment with the test agents (at IC_{50}) and complementary DNA (cDNA) was synthesized. Real-time polymerase chain reaction (PCR) was performed in which 1 μl cDNA was added to 96-well plates in duplicate. Reaction mix containing COX-2 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) primers was added and PCR was performed. The threshold cycle (C_t) was calculated and COX-2 messenger RNA (mRNA) expression was normalized for GAPDH.

Results:

Cell line	COX-2 mRNA levels (ΔC_t)			In vitro proliferation (IC_{50} ($\mu\text{mol l}^{-1}$))	
	Control	NS398	Aspirin	NS398	Aspirin
C17OIM2	1.2	0	6.4	200	3250
HCT116	10.0	0	36.0	150	3250
HT29	1.0	0	15.0	300	4200

The *in vitro* sensitivity of the cell lines to NS398 appeared to relate to the level of COX-2 gene expression, with HCT116 expressing the highest levels of COX-2 mRNA. *In vitro* treatment of the human colonic tumour cell lines with aspirin and NS398 resulted in upregulation and downregulation of

COX-2 mRNA levels respectively, as quantified by real-time PCR.

Conclusion: These data suggest that COX-2 selective inhibitors may act at the gene level resulting in antiproliferative effects. Aspirin increased COX-2 gene expression, and its antiproliferative action may be independent of its effect on COX-2.

Identification of significant novel genetic aberrations in colorectal cancer using comparative genomic hybridization

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Background: Current models suggest that colorectal cancer is initiated by and progresses through the activation of oncogenes and the suppression or loss of tumour suppressor genes (TSGs). The technique of comparative genomic hybridization (CGH) allows copy number change across the entire genome to be identified, highlighting areas of tumour copy number gain and loss representing both known and potential novel oncogenes and TSGs.

Methods: CGH was performed on 40 colorectal primary tumours.

Results: CGH identified a large number of genetic aberrations; tumours had a median (range) of 6.5 (0–19) amplifications and 8 (0–21) deletions. Frequent amplifications included minimal regions of involvement loci at 13q21–22 in 53 per cent of cases ($n=21$), 20q1–ter in 43 per cent ($n=17$), 8q21 in 37 per cent ($n=15$), 2q24 in 35 per cent ($n=14$), 12q13–21 in 30 per cent ($n=12$), 7p12 in 27 per cent ($n=11$) and 6q12–16 in 23 per cent ($n=9$). Frequent deletions included minimal regions of involvement loci at 1p35–ter in 55 per cent of cases ($n=22$), 17p13 in 43 per cent ($n=17$), 8q21 in 40 per cent ($n=16$), 22q13 in 50 per cent ($n=20$), 9q32–ter in 33 per cent ($n=13$), 16q22 in 33 per cent ($n=13$), 10q2–ter in 27 per cent ($n=11$) and 8p22–ter in 30 per cent ($n=13$). The 8p22–ter deletion was associated with significantly shorter survival ($P=0.04$, log rank test). Deletion at this locus has previously been noted in prostate, lung and colorectal cancer, and is considered to harbour a candidate TSG but has not previously been shown to have prognostic significance in colorectal cancer. Tumours with a deletion at 10q25–ter or an amplification at 13q21–22 were more likely to be moderately or poorly differentiated ($P=0.04$ and $P=0.02$ respectively, Fisher's exact test). The 10q25–ter region harbours the loci for the caspase 7 gene and the putative 'deleted in endometrial cancer' (DEC) TSG. The high frequency of a deletion in the 1p35–ter region remains unexplained with the *p73* tumour suppressor gene (which locates to within this region) proposed. Areas of well characterized aberration in colorectal cancer such as *p53* (17p13), *DCC* (18q21) and *c-MYC* (8q24) were also frequently identified. Tumours harbouring a deletion at the *p53* locus ($n=17$) demonstrated more genetic amplifications (median 4

versus 10; $P=0.005$) and deletions (median 5 *versus* 12; $P<0.001$, Mann-Whitney U test) than tumours with no deletion at this locus.

Conclusion: In addition to identifying areas of known abnormality in colorectal cancer, this large series of CGH identified several novel loci, some of which have prognostic and phenotypic significance and therefore warrant further investigation.

BAT-26 microsatellite instability is a sensitive indicator of mismatch repair mutation in hereditary non-polyposis colorectal cancer

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Background: Hereditary non-polyposis colorectal cancer (HNPCC) is due to inactivation or mutation of one of the mismatch repair (MMR) proteins responsible for correction of DNA replication errors. Most kindreds conforming to the Amsterdam criteria of HNPCC have an identified mutation of the mismatch repair genes *bMLH1* or *bMSH2* but the identification of MMR mutations is time consuming, expensive and may be unreliable. Microsatellite instability (MSI), seen as changes in allele length after polymerase chain reaction amplification, can be used as a marker of MMR deficiency.

Methods: The efficiency of a panel of microsatellite markers (BAT-26, BAT-25, D2S123, D5S346 and D17S250) was assessed to identify MSI in sporadic colorectal cancer controls and patients referred to the Wessex regional genetics service. Patients with a strong family history of colorectal cancer had genetic testing for MMR status of *bMLH1* and *bMSH2*. Tumour and normal mucosal DNA was extracted from formalin-fixed, paraffin-embedded tissue. Polymerase chain reaction products were visualized by polyacrylamide gel electrophoresis, ethidium bromide staining and ultraviolet illumination.

Results: BAT-26 allele shortening was seen in seven of nine families with a known MMR mutation and in 11 of 22 patients who fulfilled the Amsterdam criteria of HNPCC. Instability of the other four microsatellites was identified only in the presence of BAT-26 instability. Nine of ten controls with sporadic cancer were microsatellite stable at the five loci examined as were 24 of 25 patients with a family history of cancer not fulfilling the Amsterdam criteria.

Conclusion: The microsatellite marker BAT-26 is the most sensitive indicator of the five microsatellites examined for MMR mutation and used alone will identify approximately 80 per cent of families with germline mutations.

Changes in serum soluble fms-like tyrosine kinase 1 and endothelium-specific receptor tyrosine kinase receptors in colorectal cancer following surgical resection

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Background: Angiogenesis is essential to the growth of solid tumour. Soluble fms-like tyrosine kinase 1 (sFLT-1) and soluble endothelium-specific receptor tyrosine kinase (sTIE-2) receptors are the natural receptors of vascular endothelial growth factor and angiopoietin respectively in the circulation. This study aimed to compare the serum levels of sFLT-1 and sTIE-2 receptors in patients with colorectal cancer and normal controls, and their kinetics after tumour resection.

Methods: Forty-five patients undergoing resection for colorectal cancer (37 curative, eight palliative; seven Dukes A, ten Dukes B, 20 Dukes C, eight Dukes 'D') and 29 healthy controls were recruited. Serum levels of sFLT-1 and sTIE-2 receptors were assayed by quantitative sandwich enzyme-linked immunosorbent assay before and 4–6 h after operation. The minimum detectable level of sFLT-1 and sTIE-2 receptors was 0.2 and 1 ng ml⁻¹ respectively.

Results: sFLT-1 receptors were detected in ten of 37 and one of eight patients with colorectal cancer before curative and palliative resection respectively, and in 19 of 29 normal controls. The level of sTIE-2 receptors was significantly raised in patients with colorectal cancer compared with normal controls (median 57.7 *versus* 48.6 ng ml⁻¹; confidence interval (c.i.) – 13.5 to – 3.3 ng ml⁻¹, $P=0.0018$). Patients who had undergone curative resection demonstrated a significant increase in postoperative sFLT-1 level compared with the preoperative value (c.i. – 0.0 to 0 ng ml⁻¹, $P=0.03$), while there was no significant increase after palliative resection (c.i. – 0.1 to 0 ng ml⁻¹, $P=0.12$). The serum level of sTIE-2 receptor demonstrated a more significant decrease in patients undergoing curative (c.i. 9.9–20.3 ng ml⁻¹, $P<0.0001$) than palliative (c.i. 0.5–35.9 ng ml⁻¹, $P=0.05$) resection. Preoperative levels of sTIE-2 receptor were significantly higher in patients who presented with metastases than those without (median 70.7 *versus* 56.9 ng ml⁻¹; c.i. – 25.4 to – 2.0 ng ml⁻¹, $P=0.019$). There was a positive correlation between the preoperative sFLT-1 and sTIE-2 receptor levels ($\rho=0.37$, c.i. 0.09–0.60, $P=0.01$, Spearman's rank correlation test).

Conclusion: Serum sFLT-1 receptor levels were suppressed and serum sTIE-2 receptor levels were raised in patients with colorectal cancer. The decrease in sTIE-2 receptor levels after operation indicates that the main source of sTIE-2 receptors may be the tumour load, possibly predicting oncological clearance in patients with colorectal cancer. Both soluble receptors may play an important role in tumour angiogenesis.

PAP, a regeneration-associated gene, is overexpressed in colorectal carcinoma

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Background: The pancreatitis-associated protein (*PAP*) gene is a member of the regenerating (*REG*) gene superfamily and is expressed in hepatocellular carcinoma, pancreas and normal mucosa of the small intestine but not the large intestine. It has been reported previously that *REGIA* expression in colorectal cancer (CRC) is an independent marker of recurrence following curative resection of the primary tumour. This study examined the expression of *PAP* in CRC and the role of this gene in determining prognosis after a curative resection.

Methods: Expression of *PAP* messenger RNA was evaluated by reverse transcription-polymerase chain reaction (PCR) in 129 CRC and 72 adjacent histologically normal mucosa samples from patients who underwent resection of CRC and for whom long-term follow-up data were available. PCR products were confirmed by direct sequencing. Survival analyses were performed according to the method of Kaplan and Meier.

Results: *PAP* transcripts were detected in a significantly greater proportion of CRC than normal mucosa samples (70 versus 43 per cent; $P < 0.001$). The prevalence of *PAP* expression was independent of the age and sex of the patients as well as the site and pathological stage of the primary cancer. The 5-year survival rate of patients whose tumours expressed *PAP* was similar to that of patients with *PAP*-negative tumours (both 56 per cent; $P = 0.93$). Survival characteristics according to *PAP* expression were also similar when patients were stratified by Dukes stage.

Conclusion: Like *REGIA*, *PAP* is overexpressed in CRC; this is consistent with the notion that genes associated with regeneration play a critical role in colorectal carcinogenesis. Expression of *PAP* in cancer-associated mucosa suggests that this gene may serve as an intermediate biological marker of field change in the colorectum. The survival data imply diverse biological roles for various *REG* gene homologues in determining the aggressiveness of CRC.

Intraoperative local hypoxia facilitates detachment of viable colon cancer cells

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Background: Tumour cells when rendered hypoxic have an enhanced ability to form metastases. The carbon dioxide pneumoperitoneum used in laparoscopic surgery as well as newer gases like helium cause relatively hypoxic conditions. These relatively hypoxic conditions may enhance port-site metastasis. This study aimed to investigate the changes in colon

cancer cell adhesion brought about by the hypoxic stress of both carbon dioxide and helium pneumoperitoneum.

Methods: Cells from the human colonic cancer cell line SW1222 were exposed to an *in vitro* pneumoperitoneum of either air (control), carbon dioxide or helium at 3 mmHg for 4 h at 37°C. Preprepared 96-well plates coated with either Matrigel (reconstituted basement membrane), collagens I and III, fibronectin or gelatin were used for adhesion assays (Stratech, UK). After gas exposure, the cells were formed into a cell suspension in serum-free medium. Each plate was divided into three groups (air, helium, carbon dioxide), 1×10^5 cells were added to each well and the plates were then incubated for 1 h at 37°C. The remnant cell suspensions were replaced into culture flasks and exposed to a 4-h air pneumoperitoneum to allow reoxygenation to occur. The 96-well plates were then washed with phosphate-buffered saline, 100 µl of medium was added and remnant adherent cell number was estimated using a non-radioactive methyl tetrazolium salt cell proliferation assay. The wells were read spectrophotometrically. The adhesion of cells in both the carbon dioxide and helium groups was expressed as a percentage of control. The measurements were repeated for the cells after the 4-h air reoxygenation pneumoperitoneum.

Results:

	Cell adhesion (% air control)			
	Carbon dioxide (n=96)	Carbon dioxide and reoxygenation	Helium (n=96)	Helium and reoxygenation
Matrigel	55*	96†	84*	110‡
Collagen I	73*	103†	93*	99‡
Collagen III	77*	101†	90*	105‡
Fibronectin	65*	91†	80*	97‡
Gelatin	75*	105†	85*	117‡

* $P < 0.05$ versus air, † $P < 0.05$ versus carbon dioxide, ‡ $P < 0.05$ versus helium (analysis of variance)

Conclusion: Carbon dioxide and helium pneumoperitoneum reduces tumour cell adhesion in a non-specific fashion. This response could explain tumour cell detachment during surgery. Reoxygenation makes cells more adhesive. This model may provide a mechanism to explain how viable tumour cells detach from a primary lesion and establish metastatic foci. The effect is greater for carbon dioxide than helium.

Pelvic floor weakness develops after menopause-related reduction in pelvic connective tissue resilience

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Background: Menopause is a stronger predictor of uterosacral ligament resilience than parity. The mechanisms could include repeated stretching of pelvic ligaments by increased pelvic floor movement after childbirth or menopause-related hormonal changes reducing ligament resilience and pelvic floor support. This study assessed the relationship between menopause, uterosacral ligament resilience and pelvic floor descent.

Methods: Patients without a history of pelvic floor prolapse underwent dynamic magnetic resonance pelvic floor imaging before hysterectomy for benign uterine conditions. Pelvic floor descent was defined as the distance of uterocervical junction movement in relation to the line between the inferior pubic symphysis border and the last fixed sacral segment. This distance was measured at rest and straining. The uterosacral ligament was removed from the hysterectomy specimen and the resilience determined by constant speed tensiometer.

Results: Twenty-one patients (mean(s.d.) age 49(12) years) were studied.

	Premenopausal (n=12)	Postmenopausal (n=9)	P*
Uterosacral resilience (J)	0.029(0.014)	0.012(0.013)	0.017
Pelvic floor descent (cm)	1.04(0.78)	1.74(1.76)	n.s.

Results are expressed as mean(s.d.) n.s., Not significant. *Mann-Whitney U test

There was a weak correlation ($r = -0.31$, $P = 0.17$, Pearson test) between uterosacral ligament resilience and pelvic floor descent.

Conclusion: Uterosacral ligament resilience and pelvic floor descent were related, but only uterosacral ligament resilience deteriorated significantly with menopause. This finding suggests that pelvic floor weakness develops after menopause-related changes in pelvic floor connective tissue resilience.

Immunoresponsiveness in metastatic colorectal cancer during anticarcinoembryonic antigen vaccination

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Background: The use of monoclonal murine anticarcinoembryonic antigen (anti-CEA) antibodies is safe in patients with advanced colorectal cancer. PR1 A3 is such an antibody, used extensively in radioimmunoscintigraphy, which binds only to cell-based CEA and not to soluble circulating CEA.

Methods: Twelve patients with metastatic PR1 A3-binding colorectal cancers were vaccinated intradermally over a 3-month period. Idiotypic cascades were detected by enzyme-linked immunosorbent assay (ELISA) against the fragment for antigen binding of the parent antibody and a recombinant peptide containing the PR1 A3 epitope. Anti-CEA antibodies

were assessed by ELISA and flow cytometry with a CEA-transfected murine rectal carcinoma line, using humanized antibodies as controls. Peripheral blood and mesenteric lymph node lymphocytes were extracted for flow cytometric subpopulation analysis, measurement of interleukin (IL) 2 receptor expression and tritiated thymidine incorporation with cytokine estimations of phytohaemagglutinin-stimulated co-cultures for IL-2, IL-4 and interferon (IFN) γ .

Results: All patients developed detectable anti-idiotypic antibodies; no patient generated autoanti-idiotypic antibodies or anti-CEA antibodies. Lymph nodes showed a high percentage of pre-existing natural killer cells, IL-2 receptor-expressing T cells and B cells. In all cases peripheral lymphocyte proliferation was subnormal before treatment and reverted to normal during therapy. Mesenteric nodal lymphocyte responses to mitogens were equivalent to those of pretreatment peripheral lymphocytes. CEA responses and PR1 A3 responses were significantly greater (18.69 and 9.06 times activity respectively). IL-2 and IFN- γ production was subnormal before treatment, reverting to normal in all patients during immunization ($P < 0.001$). Pretreatment IL-4 production was normal but fell to subnormal levels during therapy ($P < 0.001$). IL-2 receptor expression by CD4-positive peripheral lymphocytes in PR1 A3 coculture rose from 4.6 to 26.2 per cent during therapy ($P < 0.001$).

Conclusion: PR1 A3 results in antigen-specific alteration of the lymphocyte cytokine profile with IL-2 receptor production. Pre-existing draining lymph node lymphocytes appear pre-sensitized to CEA with large subpopulations of immunocompetent effector cells, suggesting a functional defect in antigen presentation.

Preoperative radiotherapy leads to overexpression of type IV collagenases in rectal cancer

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Background: Overexpression of type IV collagenases (matrix metalloproteinases (MMPs) 2 and 9) has been shown to correlate with Dukes stage, metastatic potential and shorter disease-free interval in colorectal cancer. Preoperative high-dose radiotherapy is increasingly used as adjuvant treatment for patients with resectable rectal cancer. This study aimed to determine the effect of preoperative high-dose radiotherapy (25 Gy in five fractions in a week) on the type IV collagenase protein profile in patients with resectable rectal cancer.

Methods: Biopsy samples of tumour and normal mucosa from 12 patients with resectable rectal cancer were obtained before and after radiotherapy. Expression of the type IV collagenases (both pro and active forms) was studied using gelatin zymography. Enzyme levels were normalized for the total protein content of each sample.

Results: Rectal cancer specimens expressed both pro (72 kDa) and active (62 kDa) forms of MMP-2 but only the pro form of

MMP-9 (92 kDa). Normal mucosal specimens showed expression of the pro forms of MMP-2 and MMP-9 while no active form was detected in any of the samples. A significant threefold to fourfold increase ($P < 0.01$) in active MMP-2 (62 kDa) was seen in rectal cancer after radiotherapy. Radiotherapy also led to a twofold increase ($P = 0.047$) in pro MMP-2 (72 kDa) and a twofold to threefold increase ($P = 0.03$) in the precursor form of MMP-9 (92 kDa). In contrast, no significant change in the levels of the normal mucosal precursor MMP-2 and MMP-9 was noted.

Conclusion: Preoperative high-dose radiotherapy leads to an increase in the activity of type IV collagenases in patients with resectable rectal cancer. This increase may be responsible for establishing both a blood supply and the invasive edge of the remaining viable cancer cells in the pelvis, enhancing recurrence. Type IV collagenase inhibition may be an additive therapeutic adjunct to radiotherapy in rectal cancer.

Role of hypermethylation of the *hMLH1* promoter region in hereditary non-polyposis colorectal cancers versus sporadic replication error-positive colorectal cancers

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Background: Hypermethylation of the promoter region of the *hMLH1* gene is associated with absent expression of MLH1 protein in sporadic replication error (RER)-positive colorectal cancers, and it has been proposed that methylation may be a third pathway in Knudson's hypothesis. The incidence of hypermethylation of the *hMLH1* promoter in hereditary non-polyposis colorectal cancer (HNPCC) and sporadic RER-positive colorectal cancers was investigated.

Methods: DNA was available from nine patients with HNPCC (median age 57 (range 39–67) years) and nine with sporadic RER-positive colorectal cancer (median age 76 (range 41–85) years). The RER status was determined by amplification of the microsatellite gene locus BAT26. The *hMLH1* and *hMSH2* genes were directly sequenced to search for possible mutations. The methylation status of the *hMLH1* promoter was studied by the polymerase chain reaction-based HpaII restriction enzyme assay technique.

Results: All cases were confirmed as RER positive. Mutations in *hMLH1* were found in all nine HNPCC cases: a 3.5-kilobase genomic deletion comprising exon 16 in six and a splice site mutation at exon six in three cases. There were no mutations detected in the sporadic RER-positive cases. The promoter region was hypermethylated in six of nine sporadic RER-positive cases versus none of nine HNPCC cases ($P < 0.007$).

Conclusion: While mutations are responsible for the RER-positive phenotype in HNPCC, the *hMLH1* promoter was

hypermethylated in the majority of sporadic RER-positive cases. These data further support the argument that tumours from patients with HNPCC, which almost always acquire a raised mutation rate, mostly follow a different pathway from sporadic RER-positive tumours.

Polytetrafluoroethylene versus heparin-bonded Dacron for prosthetic femoropopliteal bypass

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Background: Dacron was largely abandoned for femoropopliteal bypass 30 years ago as saphenous vein achieved better patency rates. Patency in prosthetic above-knee (AK) femoropopliteal bypass in patients on aspirin is equivalent to that with saphenous vein. Heparin-bonded Dacron (HBD) and polytetrafluoroethylene (PTFE) have been compared in a randomized clinical trial, which also included below-knee (BK) popliteal or tibioperoneal trunk bypass when the long saphenous vein was absent or inadequate.

Methods: A multicentre study was performed involving ten hospitals over a 28-month recruitment period. Two hundred and nine patients undergoing femoropopliteal bypass (180 AK, 29 BK) were randomized to HBD ($n = 106$) or PTFE ($n = 103$). Aspirin 300 mg day⁻¹ was started before operation and was continued unless the patient was intolerant.

Results: Mean follow-up was 34 (range 19–48) months. Fifteen patients (7 per cent) have died with patent grafts and three infected grafts (1 per cent) were removed. Patency (measured by Kaplan–Meier survival analysis) was 70, 63 and 55 per cent at 1, 2 and 3 years for HBD, compared with 56, 46 and 42 per cent respectively for PTFE ($P = 0.0444$). Patency at 3 years for AK bypass was significantly better than that for BK bypass. A total of 70 further interventions were performed on 47 patients achieving long-term patency in only three. Amputations were performed in 23 patients, six with HBD and 17 with PTFE ($P = 0.015$; Fisher's exact test).

Conclusion: After femoropopliteal bypass, HBD had a better primary patency than PTFE and had a lower amputation rate.

Natural antioxidants albumin and bilirubin, smoking and peripheral vascular disease

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Background: Epidemiological studies have shown that the level of serum bilirubin, a naturally occurring antioxidant, is lowered in men with ischaemic heart disease. The assumption is that

bilirubin is scavenged by free oxygen radicals. The aim was to test the hypothesis that bilirubin would be lowered from a normal population mean of $12 \mu\text{mol l}^{-1}$ in patients with peripheral vascular disease (PVD). Serum albumin, another naturally occurring antioxidant, was also investigated.

Methods: A prospective study was carried out from January 1994 to December 1998. Male subjects were recruited from a joint cardiovascular risk factor management clinic. Patients with impaired renal function, diabetes or with abnormal liver or thyroid function were excluded. Patients with PVD were claudicants with an ankle: brachial pressure index of less than 0.9. The control population comprised asymptomatic patients with hyperlipidaemia.

Results: Results are expressed as mean(s.d.). Serum bilirubin was lowered in the control group by smoking, which produces free radicals (smokers ($n=36$) $8.2(3.5) \mu\text{mol l}^{-1}$ versus non-smokers ($n=119$) $9.9(3.4) \mu\text{mol l}^{-1}$; $P=0.01$, unpaired t test). This effect was also observed in patients with PVD (smokers ($n=31$) $6.9(3.4) \mu\text{mol l}^{-1}$ versus non-smokers ($n=42$) $9.1(4.3) \mu\text{mol l}^{-1}$; $P=0.02$). This pattern was repeated with albumin in both controls (smokers $47.3(3.1) \text{ g l}^{-1}$ versus non-smokers $48.5(3.2) \text{ g l}^{-1}$; $P=0.05$) and PVD (smokers $46.1(2.7) \text{ g l}^{-1}$ versus non-smokers $47.7(3.2) \text{ g l}^{-1}$; $P=0.03$). Excluding smokers, patients with PVD had a lower bilirubin level than controls (9.1 versus $9.9 \mu\text{mol l}^{-1}$) and, although this was not significant, this was below the normal population mean of $12 \mu\text{mol l}^{-1}$. The same pattern was seen with albumin (47.7 versus 48.5 g l^{-1}). Frequency analysis of bilirubin levels one standard deviation below the control mean confirmed that a higher proportion of patients with PVD had a serum bilirubin level of $6 \mu\text{mol l}^{-1}$ or lower (17 of 42 versus 27 (23 per cent) of 119 for controls; $P=0.04$, Fisher's test).

Conclusion: The natural antioxidants bilirubin and albumin are lowered in PVD as well as by smoking. This finding supports the hypothesis that bilirubin is a free radical scavenger. The role of bilirubin and albumin in therapeutic or diagnostic strategies has yet to be defined.

Compliance of laser tissue soldered anastomoses in vivo

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Background: The compliance of an anastomosis is a predictive factor for long-term patency of a graft or vascular reconstruction. This study compared the compliance of manual suture and laser tissue solder (LTS) anastomosis in an end-to-end model.

Methods: Twelve large white Landrace pigs (mean(s.d.) $25(4) \text{ kg}$) were used. The common carotid artery (CCA) was anastomosed using one of the following methods: (1) LTS ($n=4$), (2) continuous suture (CS) ($n=4$) and (3) CS plus LTS reinforcement ($n=4$). The vessel wall motion was recorded using an ultrasound echo-locked walltracking system. Diame-

trical compliance was then calculated. Postanastomotic CCA blood flow was measured. The animals were kept and later killed for histological evaluation.

Results: The Table shows the compliance profile of anastomosis versus distance along the CCA. The anastomosis is at 0 mm. The positive distance values are towards the head.

	Distance along vessel (mm)								
	-11	-8	-5	-2	0	2	5	8	11
LTS	28	27	35	30	18	29	33	28	26
CS	25	24	38	31	7	27	37	23	22
CS+LTS	24	25	41	38	5	19	31	36	20

Values are mean compliance

There was a significant reduction in compliance at the anastomosis with all three techniques ($P<0.05$, Student's t test). The reduction in vessel elasticity at the anastomosis generated para-anastomotic hypercompliant zones 5 mm before and after the anastomosis. The compliance reduction was less with the LTS than the CS technique ($P<0.001$). There was no significant difference in compliance between CS alone and CS plus LTS reinforcement at the anastomosis ($P=0.56$). The mean blood flow after anastomosis was 137, 141 and 127 ml min^{-1} in the LTS, CS and CS+LTS groups respectively.

Conclusion: Anastomotic compliance was greater in LTS than CS anastomoses. Reinforcement of CS anastomoses using LTS did not adversely affect anastomotic compliance.

Measuring the morphometric response of renal arteries to a selection of stents

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Background: This study aimed to measure the tissue response of renal arteries to intraluminal stents.

Methods: Twenty-two stents, 16 renal artery memotherm (RAM), two applied vascular engineering (AVE), two Palmaz and two femoral memotherm stents, were placed in the renal arteries of 12 large white female pigs, with two control vessels. Angiography was undertaken at stent insertion and 6 weeks later at explantation. All procedures were carried out under the Animals (Scientific procedures) Act of 1986, with appropriate project and personal licences. Renal arteries with the stent *in situ* were fixed in 4 per cent formalin and embedded in resin (t8100; Kulzer Histo-technik). The embedded stents were sectioned using a precision saw (Isomet 2000; Beuhler Krautkramer) and the slides stained with haematoxylin and eosin or for alpha smooth muscle actin. Sections were examined under a microscope (Seescan; Olympus) to measure the cross-sectional area of the lumen, neointima, media and adventitia in the proximal, mid and distal thirds of each stent.

The paired *t* test was used for analysis of all stents, and the Mann-Whitney *U* test was used when comparing the RAM with other stents.

Results: The mean luminal cross-sectional areas in the proximal, mid and distal thirds of all stents were 16.48, 16.22 and 15.84 mm² respectively. Corresponding values for the neointima were 4.87, 5.30 and 10.73 mm², with significantly more neointima between proximal and distal portions of stents ($P < 0.001$). The mean values in the proximal, mid and distal portions of the AVE stent were 12.69, 9.45 and 7.48 mm² for the lumen, and 1.11, 1.93 and 1.32 mm² for the neointima. There was a significantly smaller lumen in the AVE stent than the RAM stent ($P < 0.05$) and there was less neointima ($P < 0.05$). No other differences were demonstrated between any other stents.

Conclusion: This technique of slide preparation with the stent *in situ* enables accurate measurement of tissue layers. An increase in the overall luminal diameter is associated with a greater neointimal response, with a larger net gain demonstrated in RAM stents at 6 weeks.

Effect of deep venous reflux on the results of superficial venous surgery

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Background: It is frequently stated that, in the presence of deep venous reflux, superficial venous surgery does not improve the symptoms and signs of chronic venous insufficiency. The aim of this study was to determine whether deep reflux impacts negatively on the ability of varicose vein (VV) surgery to improve disease-specific and generic quality of life (QoL).

Methods: This was a prospective study of 85 consecutive patients undergoing VV surgery. Deep reflux was defined as popliteal vein reflux exceeding 0.5 s on preoperative duplex imaging. Aberdeen VV symptom severity score (AVSS) (disease-specific) and Short Form 36 (SF-36) (generic) QoL questionnaires were completed before, and 4 weeks and 6 months after operation. The Wilcoxon test was used for statistical analysis.

Results: Patients with popliteal reflux ($n = 27$ (32 per cent); group 1) were older (median 63 (range 56–71) *versus* 57 (range 47–64) years; $P = 0.002$) and more likely to have skin changes (22 of 27 *versus* 31 of 58; $P = 0.013$) than those who did not (group 2). Before operation, there was no significant difference in AVSS or SF-36 scores between the groups. The AVSS improved significantly by 4 weeks and 6 months after surgery in both group 1 (median 25.2 before operation *versus* 18.4 after 4 weeks ($P = 0.021$) and 16.4 after 6 months ($P = 0.001$)) and group 2 (22.1 before operation *versus* 16.0 after 4 weeks ($P = 0.001$) and 9.0 after 6 months ($P = 0.001$)). The magnitude of the improvement was not significantly different between the groups. Patients in group 2, but not group 1, also showed a

small but significant improvement in SF-36 scores relating to physical functioning (75 *versus* 85; $P = 0.002$) and bodily pain (62 *versus* 82; $P = 0.001$) by 6 months after operation.

Conclusion: VV surgery is as effective in improving disease-specific QoL in patients with deep venous reflux as it is in patients with normal deep veins, despite the fact that the former are older and more likely to have the skin changes of chronic venous insufficiency. The SF-36 appears insensitive to clinically meaningful changes in QoL in this patient group.

Collagen turnover is increased in healing venous ulcers despite decreased fibroblast growth

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Background: A thick layer of fibrous tissue is invariably found in the base of non-healing venous leg ulcers. Collagen metabolism and fibroblast growth may influence ulcer healing. This study aimed to identify differences in fibroblast growth and collagen turnover in healing and in non-healing ulcers and in normal skin.

Methods: Biopsies were taken from 12 patients with rapidly healing venous leg ulcers and 11 patients with venous leg ulcers that had not healed after 12 months of compression bandaging. Lipodermatosclerotic skin and donor graft skin were also collected from the patients with non-healing ulcers. Skin was taken from 14 normal surgical patients who acted as controls. Fibroblasts were grown from the ulcer biopsies and controls. Each fibroblast cell line was cultured in triplicate in a 96-well plate and growth was measured at 0, 1, 2, 4, 6 and 8 days using a colorimetric substrate (XTT). Collagen turnover was determined in homogenized tissue samples by measuring the N-terminal peptide of collagen III (PIIINP), a marker of collagen synthesis, and hydroxyproline, a marker of collagen degradation.

Results: The time taken to grow fibroblasts from explants was similar for non-healing (median 48 (range 34–76) days) and healing (51 (range 44–76) days) leg ulcers and normal skin (49 (range 33–76) days). This time was independent of age ($r = 0.152$). Growth curves were comparable for healing and non-healing ulcers, but were significantly depressed compared with those of normal controls ($P = 0.004$, $U = 1$). Donor skin cultured from patients with non-healing ulcers also showed depressed growth curves. PIIINP and hydroxyproline levels were significantly higher in healing compared with non-healing leg ulcers ($P < 0.02$, $U = 24$).

Conclusion: Skin fibroblasts from all patients with ulcers show depressed growth compared with normal skin, suggesting a systemic defect. Patients with rapidly healing leg ulcers have evidence of increased collagen turnover. The healing of chronic venous leg ulcers might be improved by manipulating their fibroblasts to increase collagen turnover.

Venous surgery improves skin microcirculation

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Background: Venous hypertensive microangiopathy exists in venous insufficiency even in the absence of clinically obvious skin change. Venous skin damage results mainly from sustained venous hypertension during exercise. Skin microcirculation, as measured by laser Doppler flux (LDF), is increased. The reflex arteriolar constriction in response to a change from the supine to erect posture (venoarteriolar response, VAR), which serves to protect the skin from gravitational venous pooling, is diminished. This study aimed (1) to compare ambulatory skin flux (ASF) with ambulatory venous pressure (AVP) as a measure of venous hypertension during exercise and (2) to evaluate the effect of venous surgery on the skin microangiopathy with postural change and during exercise.

Methods: Postural and exercise changes in skin microcirculation were assessed using LDF. Thirty-five patients (16 men, 19 women) of mean (s.d.) age 41(6) years participated in the study. ASF was validated in ten patients with varying degrees of venous disease in comparison to AVP (group 1). Fifteen patients undergoing superficial venous surgery were recruited (group 2). Patients with deep incompetence or an ankle: brachial pressure index of less than 0.9 were excluded. Ten age-matched normal volunteers served as controls (group 3). The LDF probe was attached to the gaiter skin and the microcirculation was monitored continuously with the subject supine, standing and during a 5-min treadmill walk at 1.6 km h^{-1} . Mean supine and standing LDF were averaged over a minute before and following a change in posture and VAR was evaluated by the difference. Mean ASF was averaged over the walking period. In group 2, the study was repeated 8 weeks after operation. Results are expressed as mean (s.e.).

Results: In group 1, mean ASF showed a strong positive correlation with AVP ($r = 0.70$, $P = 0.02$). In group 2, mean ASF was 197(54) units compared with 75(6) units in group 3 ($P = 0.015$). ASF in group 2 decreased to 107(11) units after operation ($P = 0.04$). VAR increased from 8.1(4.3) units before to 18.6(8.0) units after operation ($P = 0.02$). The difference between postoperative values in group 2 and values in group 3 was not significant.

Conclusion: Skin microcirculation is increased in venous insufficiency owing to reflux. Surgical correction of reflux reduces excess skin suffusion associated with venous microangiopathy and improves the skin microcirculatory protective function of VAR.

Evaluation of venous haemodynamics using near-infrared spectroscopy

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Background: Objective haemodynamic evaluation of dysfunction and of the efficacy of treatment are desirable in phlebology.

Near-infrared spectroscopy is a novel technique for non-invasive continuous assessment of deep tissue concentration of oxyhaemoglobin and deoxyhaemoglobin (Hb) at rest and during exercise. A new application of this technique in venous haemodynamic assessment, by monitoring changes in Hb concentration, is reported. This study compared changes in calf Hb concentration with ambulatory venous pressure (AVP) in the assessment of venous haemodynamics and evaluated the haemodynamic effects of superficial venous surgery using changes in calf Hb concentration as a surrogate marker.

Methods: Twenty-five patients participated in the study. Hb indices were validated in ten subjects by comparison with AVP. The haemodynamic effect of surgical treatment was then assessed in 15 patients (ten women and five men) with isolated superficial venous insufficiency. A pair of probes (optodes) secured posteriorly over the calf muscles continuously monitored changes in Hb concentration during supine rest, standing, ten tiptoes and walking slowly for 5 min on a treadmill at 1.6 km h^{-1} . A pulse oximeter monitored heart rate and arterial oxygen saturation. AVP was measured in the first ten patients. The study was repeated 8 weeks after operation. The Hb filling time (DFT) was measured as the time taken to achieve 50 per cent (DFT 50) and 90 per cent (DFT 90) of maximum Hb on standing. Ambulatory venous retention index (AVRI) evaluated venous retention during walking. AVRI was measured as the rise from the bottom to the new plateau, divided by the fall from the baseline to the bottom. Results were expressed as mean (s.e.) and compared using the Student's paired t test. $P < 0.05$ was taken as statistically significant.

Results: AVP correlated inversely with DFT ($r = 0.69$, $r^2 = 0.47$, $P = 0.028$). Mean preoperative DFT 50 and DFT 90 were 46(7) and 158(25) s respectively. Mean postoperative values were 72(10) and 242(32) s respectively. The increases in both DFT 50 and DFT 90 following surgery were significant ($P = 0.03$). There was a positive correlation between AVRI and AVP ($r = 0.70$, $P = 0.02$). Mean preoperative AVRI by Hb and total haemoglobin (HbT) were 0.808(0.246) and 0.423(0.075) respectively. Corresponding mean postoperative AVRI were 0.315(0.069) and 0.225(0.042) respectively. Decreases in AVRI using changes in Hb and HbT after operation were significant ($P = 0.03$ and $P = 0.01$ respectively).

Conclusion: Changes in Hb concentration correlated with AVP in assessment of venous function and may be useful in the haemodynamic evaluation of treatment of venous insufficiency.

Randomized controlled trial of four-layer bandaging and simple venous surgery for venous ulceration

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Background: No randomized controlled trial exists to show whether simple venous surgery benefits healing or maintenance of healing of venous ulcers. This pilot study investigated

whether simple surgery gave additional benefit to four-layer bandaging in terms of healing rate.

Methods: One hundred and twenty-one consecutive patients with new episodes of venous ulceration were identified, of whom 45 were unfit for surgery or unwilling to be randomized. The remaining 76 patients (aged 38–89 years; 39 women) were randomly assigned to receive four-layer bandaging ($n=39$) or simple venous surgery (long and short saphenous with or without perforator veins, $n=37$). Informed consent was obtained. Ulcers of other aetiologies were excluded. All patients were followed up for a minimum of 6 months. Ulcer healing and health-related quality of life (HRQL), as defined by scores on the Short Form 36 (SF-36) and a disease-specific questionnaire (CXVUQ), were also assessed. Ethics committee approval was obtained.

Results: The two groups had similar co-morbidity and patterns of venous incompetence. There were no major complications in either group. The healing rate was 64 per cent (25 of 39) in the conservatively treated group and 68 per cent (25 of 37) in the operated group (Pearson χ^2 , $P=0.75$). There was no significant difference in the time to ulcer healing between the two treatment groups, with a median time of 83 days for surgery *versus* 98 days for bandaging (log rank statistic=0.69, $P=0.41$). The hazard ratio from the Cox regression was 0.80 (95 per cent confidence interval (c.i.) 0.46–1.39), suggesting that ulcers in the surgery group showed slightly faster healing, although this result was not statistically significant. After adjusting for duration of ulcer, size of ulcer and previous deep vein thrombosis, there was still no significant difference in time to healing between the surgery and four-layer bandaging groups (adjusted hazard ratio 0.79 (95 per cent c.i. 0.45–1.39)). There was no difference in HRQL between the two groups in the scores of either the generic or the disease-specific questionnaires.

Conclusion: This pilot study suggests that simple venous surgery gives no adjuvant benefit to four-layer bandaging in patients with venous ulceration from the point of view of healing rate and quality of life. This is a small study with low power and a larger study is required to confirm these results.

Serum vascular endothelial growth factor and carcinoembryonic antigen in follow-up surveillance of patients with colorectal cancer

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Background: Angiogenesis is essential for the dissemination and growth of metastases in colorectal cancer (CRC). Vascular endothelial growth factor (VEGF) is the most potent angiogenic cytokine. This study aimed to assess changes in serum VEGF in patients with CRC following curative resection and to compare serum VEGF with carcinoembryonic antigen (CEA) as a predictor of metastasis during follow-up surveillance of patients with CRC.

Methods: In study 1, preoperative and serial follow-up serum VEGF levels were determined in 35 patients with CRC who had undergone curative resection. In study 2, 125 patients were recruited prospectively into an intensive follow-up programme in which VEGF and CEA measurements were collected. The upper limit of normal serum VEGF at 347 pg ml^{-1} (mean $\pm$ two standard deviations) was determined from 136 normal healthy controls.

Results: In study 1, using the pattern of change of serum VEGF, serial measurements of serum VEGF during follow-up accurately predicted disease recurrence ($P=0.027$) with a sensitivity of 67 per cent, a specificity of 83 per cent, a positive predictive value of 44 per cent and a negative predictive value of 92 per cent. In study 2, eight patients developed metastases while 117 patients remained disease free. The serum VEGF level was significantly higher in patients who presented with metastases than in those who were disease free at follow-up (median $562 \text{ versus } 226 \text{ pg ml}^{-1}$; $P<0.0001$). The distribution of serum VEGF levels in patients who were disease free was comparable to that of normal controls. Serum VEGF levels were equally distributed in disease-free patients regardless of Dukes stage ($P=0.164$, analysis of variance). Levels of serum VEGF above 347 pg ml^{-1} accurately detected the metastases ($P=0.0001$). Comparison of sensitivity and specificity showed that VEGF was 100 per cent sensitive and 71 per cent specific while CEA was 97 per cent specific but only 38 per cent sensitive. In five of eight patients with recurrence the VEGF level was raised at about the same time as there was clinical change, while in three patients the increase in VEGF level preceded the change in disease status.

Conclusion: These data suggest that serum VEGF may be a useful tumour marker in the follow-up surveillance of patients with CRC.

Regional retroviral gene-directed enzyme prodrug therapy for colorectal liver metastases *in vivo*

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Background: Gene-directed enzyme prodrug therapy is a potential treatment approach for colorectal liver metastases. This study aimed to use a recombinant retroviral vector which expresses the *Escherichia coli* cytosine deaminase (CD) gene to selectively kill tumour cells in a syngeneic model of colorectal liver metastases, following treatment with the prodrug 5-fluorocytosine (5-FC).

Methods: K12 rat colon adenocarcinoma cells were transduced with a retroviral vector expressing the CD gene under the control of a CEA promoter. Expression of CD was confirmed by polymerase chain reaction and Western blotting. Tumour cell killing and the bystander effect were assessed using 3-[4,5-

dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, thiazolyl blue cytotoxicity assays. Activity of CD in transduced K12 cells was confirmed using thin layer chromatography. BDIX rats were then injected with K12 cells via the hepatic portal vein. Metastatic liver tumours were left to develop over 10 days. Vector or control was injected via the hepatic artery and twice daily intraperitoneal injections of 5-FC 500 mg kg⁻¹ or control were started after 48 h and continued for a further 7 days. The animals were then killed and tumour volumes were calculated. Treatment groups were as follows: group 1, CD + 5-FC; group 2, CD + saline; group 3, saline + 5-FC; group 4, saline + saline; group 5, control vector (β -galactosidase) + 5-FC; and group 6, β -galactosidase + saline. *In vivo* experiments were carried out under Home Office guidelines.

Results: Expression of CD in the K12 cells increased the sensitivity of these cells to the non-toxic prodrug 5-FC, decreasing the 50 per cent inhibitory concentration from 2 mg ml⁻¹ in wild-type cells to 0.055 mg ml⁻¹ in CD-transduced cells. K12-CD cells showed an *in vitro* bystander effect in the presence of 5-FC such that 40 per cent of K12-CD cells resulted in 92 per cent relative cell death. A significant reduction in tumour volume was observed in group 1 (mean(s.d.) 59(17) mm³) compared with groups 2 (464(110) mm³), 3 (448(111) mm³), 4 (481(111) mm³), 5 (918(217) mm³) and 6 (846(197) mm³) ($P < 0.002$, Mann-Whitney *U* test).

Conclusion: This gene therapy approach resulted in significant tumour volume reduction and may represent a novel treatment for colorectal liver metastases.

Inhibitor of apoptosis, survivin, predicts death from recurrent colorectal carcinoma

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Background: The successful identification of molecular genetic markers that can predict the risk of recurrence in patients with stage II colorectal cancer (CRC) will have important therapeutic implications. The authors have previously reported that expression of survivin, a novel antiapoptosis gene, may serve as a prognostic marker in these patients. The present study examined the role of survivin protein expression, in conjunction with several other prognostic factors, in predicting survival following curative resection of stage II CRC.

Methods: Using a novel monoclonal antibody, immunohistochemical expression of survivin protein was evaluated in formalin-fixed sections of 49 stage II CRCs from patients for whom follow-up data up to 8 years were available. The Cox proportional hazards regression model was used to adjust for covariates comprising age, sex, tumour site, T stage, immunohistochemical expression of P53 and BCL2 proteins as well as histopathological features, such as degree of differentiation,

lymphocytic infiltration, venous invasion and type of invading margin of the primary tumour.

Results: Survivin was expressed in 30 of 49 CRCs. Expression of survivin was independent of P53 and BCL2 expression and there was no association with age or sex of the patients or site, T stage or other histological features of the primary cancer. The 5-year survival rate of patients with survivin-positive tumours was 52 per cent compared with 94 per cent for patients with survivin-negative tumours ($P = 0.01$). On univariate analysis, expression of survivin (hazard ratio (HR) 19.5, $P = 0.02$), an infiltrative tumour margin (HR 6.9, $P = 0.04$), rectal site of the primary cancer (HR 17.9, $P = 0.007$) and T₄ stage (HR 39.3, $P = 0.02$) were associated with an increased risk of death. On multivariate analysis, expression of survivin (HR 9, $P = 0.03$) and rectal site of the primary cancer (HR 3, $P = 0.05$) were the only factors that independently predicted an increased risk of death from recurrent cancer.

Conclusion: Survivin is an independent prognostic marker in stage II CRC. Study of survivin expression in stage II CRC can identify patients who are at increased risk of death from recurrent cancer and might benefit from adjuvant therapy.

Proteinase expression is altered and tumour cell invasiveness increased by carbon dioxide pneumoperitoneum

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Background: Matrix metalloproteinases (MMPs) are over-expressed by many malignant tumours and are involved in metastasis and invasion of tumour cells. Various studies have shown that the carbon dioxide pneumoperitoneum used in laparoscopic surgery can increase postoperative tumour growth. The effect of carbon dioxide on cancer invasion is unknown. The aim of this study was to examine the effects of pneumoperitoneum on tumour cell invasion and MMP expression.

Methods: Various colon and pancreatic adenocarcinoma cells were exposed to an *in vitro* pneumoperitoneum of carbon dioxide, helium or air at 37°C. After 3 h, 1×10^5 cells from each group were then placed into the upper compartment of Boyden chambers (pore size 3 μ m) coated with Matrigel. After 72 h the cells in the upper chambers were removed and the number of cells that had passed through the membrane was assessed using the methyl tetrazolium salt assay. Invasiveness was calculated by dividing the number of cells passing through the membrane in the experimental wells by the number of cells passing through the membrane in control wells. The same cell lines were again exposed to a carbon dioxide, helium or air pneumoperitoneum for 3 h. Following this exposure the total RNA was extracted from the cells. Quantification of RNA for MMPs was performed

by competitive reverse transcriptase–polymerase chain reaction and gene expression was expressed relative to glyceraldehyde-3-phosphate dehydrogenase controls.

Results:

	Relative invasion for each cell line			
	CC531s	SW480	PSN-1	T3M4
Carbon dioxide	164*	115	241†	87
Helium	146	114	102	88
Air	100	100	100	100

* $P < 0.05$ versus air, † $P < 0.001$ versus air and helium (Bonferroni multiple comparisons test)

	Changes in gene expression*			
	CC531s	SW480	PSN-1	T3M4
MMP-9	↔	↔	↓	↓
MT-MMP	↓	↓	↓	↑
TIMP-1	↓	↓	↑	↑
TIMP-2	↓	↓	↑	↑

*Following exposure to a carbon dioxide pneumoperitoneum. ↔, No change in expression; ↑, increased expression; ↓, decreased expression, TIMP, tissue inhibitor of MMP; MT-MMP, membrane bound matrix metalloproteinase

Conclusion: Exposure of tumour cells to a carbon dioxide pneumoperitoneum resulted in greater ability to invade artificial basement membrane *in vitro* and altered the proteinase expression of the tumour cell lines. This suggests a possible mechanism whereby a carbon dioxide pneumoperitoneum increases malignant potential.

Basic fibroblast growth factor infusion increases vascularity and blood flow but also tumour growth in a model of colorectal cancer

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Background: The response of colorectal liver metastases to chemotherapy is poor, partly owing to inadequate drug penetration. Basic fibroblast growth factor (bFGF) infusion can increase vascularity, blood flow and fluorouracil uptake without an effect on tumour proliferation and growth in an experimental hooded sarcoma-N (HSN) tumour model. The HSN tumour does not express bFGF cell surface receptors but this expression may differ between tumour types. The effect of bFGF infusion in an adenocarcinoma tumour model has now been assessed.

Methods: BDIX rats were inoculated subcutaneously with DHD/K12/Tr cells (rat colonic adenocarcinoma). Test groups were infused systemically with bFGF and controls received

saline. Tumour dimensions were recorded throughout growth. At 28 days all animals were killed and vascularity (vessel count and vessel volume determined at $\times 400$ magnification), blood flow (quantitative autoradiography) and proliferation index (percentage of cells staining with antiproliferating cell nuclear antigen antibody) were determined. Tumour volume was calculated as $\pi/6[a^2 \times b]$, where a is the shorter length and b the longer length.

Results:

	Vessel count (no. mm ⁻²)	Vessel volume (%)	Proliferation index (%)	Tumour volume (mm ³)
Control	11 (10–20)	1.8 (1.3–2.0)	5 (4–6)	359 (125–515)
bFGF	36 (31–56)	6.4 (5.5–7.3)	14 (10–16)	611 (469–628)
P^*	0.009	0.009	0.037	0.076

Values are median (interquartile range). *Mann–Whitney U test

There were also significant increases in vascular length density and blood flow between bFGF-infused and control groups ($P < 0.0001$, repeated measures analysis of variance).

Conclusion: The effect of bFGF on tumour vascularity and blood flow appears to be independent of tumour type, probably owing to bFGF activation of endothelial cell receptors. The effect on tumour proliferation and growth varies between tumour types. This finding suggests that use of an appropriate angiogenic agent could stimulate endothelial cells to increase vascularity and hence cytotoxic drug uptake without increasing tumour growth.

Sulphasalazine induces oxidative stress in colorectal cancer cells *in vitro*

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Background: The incidence of colorectal cancer in patients with inflammatory bowel disease (IBD) treated with long-term sulphasalazine (more than 3 months) was lower than that in those not treated and even than that in the general population. This effect has been found in epidemiological studies in the UK and two Scandinavian countries. The therapeutic effects of sulphasalazine in IBD are due in part to scavenging of free radicals liberated from activated neutrophils. Sulphasalazine is also thought to be an antioxidant. At different doses, several antioxidants have been shown to become pro-oxidant. The aim of this study was to evaluate the direct effect of sulphasalazine, at levels found in the body, on the intracellular redox status of colorectal cancer cells Colo 201 and Colo 205.

Methods: Colo 201 and Colo 205 cells, which proliferate in suspension, were used in this study. The cells were cultured with sulphasalazine 10^{-6} – 10^{-2} mol l⁻¹ for 24 h. Cells were also cultured with sulphasalazine 25 μ mol l⁻¹ and 1 mmol l⁻¹ over

48 h. At the designated time, the cells were labelled with 2,7 dichlorodihydrofluorescein (DCF) and propidium iodide. Controls were treated with solvent ammonium hydroxide and antioxidant N-acetyl cysteine. Above these concentrations of sulphasalazine, there was greater than 50 per cent cell death.

Results: Sulphasalazine at all tested concentrations was pro-oxidant, maximally at approximately 8 h, after which oxidant levels fell. Irreversible nuclear DNA damage signifying death was noted at above 0.5 mmol l^{-1} .

Maximum fluorescent DCF oxidation change during 48 h				
	Vitamin E 2.5 mmol l^{-1}	N-acetyl cysteine 25 mmol l^{-1}	Sulphasalazine $25 \mu\text{mol l}^{-1}$	Sulphasalazine 1 mmol l^{-1}
Colo 205	-6.5	-19	+6.2	+6.4
Colo 201	-2	-11	+7	+8.5

Conclusion: Sulphasalazine toxicity to Colo 201 and Colo 205 cells may be due to oxidative stress. Oxidative injury is a mode of action of chemotherapeutic agents and this injury occurs at small doses of sulphasalazine. Further studies are required to determine any adjunctive effect.

Endothelin ET_A receptor antagonism decreases colorectal cancer cell growth

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Background: Endothelin (ET) 1, a vasoactive peptide acting via receptors ET_A and ET_B , is overexpressed in human cancers, including colorectal cancer. Although ET-1 stimulates colorectal cancer cell growth *in vitro*, its mechanisms of action are unknown.

Methods: The effect of ET-1 and receptor antagonists (A-127722 for ET_A ; BQ788 for ET_B) on human colorectal cancer cell (LIM1215, SW620) and rat cancer cell (MC28) growth was measured using a methylene blue assay. Mechanisms of growth were studied by assessing (1) apoptosis, detecting Annexin V binding flow cytometrically and (2) cell proliferation, detecting 5-bromo-2'-deoxyuridine (BrdU) incorporation immunocytochemically.

Results: ET-1 stimulated growth in all cells, reaching significance at 10^{-7} – $10^{-8} \text{ mol l}^{-1}$ ($P < 0.05$). This effect was reversed by A-127722 ($10^{-11} \text{ mol l}^{-1}$; $P < 0.05$), but not by BQ788. In parallel cultures, apoptosis was similar in controls and cells treated with ET-1 with or without antagonist (10–15 per cent fluorescent units, all cultures). BrdU staining demonstrated an ET-1-dependent increase in cell proliferation, which was reversed by A-127722 (14 (range 13–15), 7 (6–7) and 14 (12–16) per cent stained cells above baseline for LIM1215, SW620 and MC28 cells respectively; $P < 0.05$).

	LIM1215 + ET-1	SW620 + ET-1	MC28 + ET-1
48 h	1.13(0.10)	1.14(0.09)	1.17(0.14)
72 h	1.14(0.10)	1.35(0.13)	1.20(0.12)

Values are mean(s.d.) methylene blue absorbance units (650 nm) expressed as a ratio of control value; control mean values = 1.0 (s.d. for controls always < 0.07).

Conclusion: ET-1 stimulates human colorectal and rat cancer cell growth *in vitro*. This effect is reversed by an ET_A but not by an ET_B receptor antagonist. Cell growth is a direct consequence of an increase in cell proliferation rather than a reduction in apoptosis.

Overexpression of gastrin-releasing peptide receptors by human colonic tumours

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Background: Gastrin-releasing peptide (GRP) is a neuropeptide expressed throughout the human gut. GRP receptor (GRP-R) expression has been implicated in the pathogenesis of a number of human carcinomas. This study aimed to quantify GRP-R expression in human colonic adenomas, in carcinomas and in normal mucosa from these patients.

Methods: A polyclonal rabbit antihuman GRP-R antibody was raised, purified and characterized. Standard immunohistochemistry, following antigen retrieval, was used on sections of formalin-fixed, paraffin-embedded human colonic tumours and mucosa. The degree of mucosal staining was graded independently by three observers (no staining (–), equivocal staining ($\pm$), low-level staining (+), moderate staining (++) or high-level staining (+++)).

Results: To date 15 normal mucosal samples, 16 adenomas and 12 colon carcinomas have been studied. The median level of reported staining is shown in the Table. Equivocal or low-level GRP-R staining was demonstrated in 11 of 15 normal mucosal samples. A moderate to high level of staining was demonstrated in nine of 16 colonic adenomas and eight of 12 carcinomas. Where normal mucosa was also present for comparison, the level of expression was always greater in the adenoma or carcinoma.

	Tissue GRP-R staining				
	–	$\pm$	+	++	+++
Normal mucosa	4	7	4	0	0
Adenoma	2	2	3	4	5
Carcinoma	0	0	4	6	2

Conclusion: GRP-R is expressed in normal colonic mucosa at low levels. Overexpression is a frequent, early event in the human colonic adenoma–carcinoma sequence. GRP-R over-

expression may be important in the regulation of colonic mitogenesis and/or morphogenesis.

Hypermethylation of the promoter region of the E-cadherin gene (*CDH1*) in sporadic and ulcerative colitis-associated colorectal cancer

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Background: Ulcerative colitis-associated colorectal cancer (UCACRC) has several distinctive clinicopathological and genetic features which differ from those of sporadic colorectal cancer (SCRC). Hypermethylation of the E-cadherin gene (*CDH1*) has not been described previously in colorectal cancer. A panel of SCRCs and UCACRCs were investigated for mutations in *CDH1* and for hypermethylation of its promoter region.

Methods: DNA was available from 14 patients with UCACRC and 14 patients with SCRC. All exons of *CDH1* were amplified with the polymerase chain reaction (PCR) and screened using single-strand conformational polymorphism and direct sequencing. Hypermethylation of the *CDH1* promoter region was determined by methylation-specific PCR following bisulphite modification, and compared with E-cadherin protein expression from a previous immunohistochemical study.

Results: Thirteen of the 28 cancers were hypermethylated in the *CDH1* promoter region, eight of 14 in the UCACRC group and five of 14 in the SCRC group (*P* not significant); this correlated with reduced E-cadherin expression (*P* < 0.05). There was a trend for methylation to be associated with a more advanced stage of cancer, although this did not reach statistical significance. There were no mutations in *CDH1* in either group although there were several polymorphisms.

Conclusion: Hypermethylation of the promoter region in *CDH1* was demonstrated in 13 of the 28 colorectal cancers studied. There was no difference between the UCACRC and SCRC groups. Just as there are specific differences in the genetic changes between UCACRC and SCRC, there is also likely to be a large degree of overlap among the genetic pathway of these cancers.

Low molecular weight heparin therapy significantly delays endochondral ossification during fracture healing

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Background: Low molecular weight heparin (LMWH) is gold standard thromboprophylaxis in both emergency and elective orthopaedic surgery. Many cytokines regulating fracture

revascularization are heparin dependent and long-term LMWH therapy causes osteopenia. Endothelial cells (ECs) disassociate to become osteoprogenitor cells in endochondral ossification. It was hypothesized that LMWH therapy alters this vascular disassembly and thus delays bone formation during fracture healing.

Methods: Thirty-six mature male rabbits underwent fracture of bilateral floating ribs under anaesthesia and were randomized to either treatment with LMWH (2 mg in 400 µl subcutaneously per day) or control (saline 400 µl day⁻¹ subcutaneously). Six animals from each group were killed at days 3, 7 and 14 after fracture and the rib specimens were excised. Callus index was measured. Specimens were fixed, decalcified and sectioned. Fibrin clot, callus maturity and interfragmentary mesenchymal cell proliferation were graded using haematoxylin and eosin staining. Blood vessel proliferation and immaturity indices were determined immunohistochemically using monoclonal antibodies to CD31, Ki67 and alpha smooth muscle actin respectively. Transforming ECs were identified by distinct morphology.

Results: Daily LMWH therapy resulted in a significant reduction in callus size, medullary cellular response, endothelial and perivascular cell transformation and endochondral ossification compared with control.

	Control			LMWH		
	Day 3	Day 7	Day 14	Day 3	Day 7	Day 14
Callus index	—	1.6	2.1	—	1.4*	1.9*
Callus maturity (grade)	1	3	6	1	2*	4*
Medullary response (per field)	75(7)	186(41)	—	56(3)*	107(20)*	—
EC transformation (per field)	—	47(8)	65(5)	—	22(4)*	36(3)*
Fibrin clot (mm ²)	1.5(0.2)	—	—	2.8(0.4)*	1.0(0.1)*	—

Values are mean(s.e.m.) (*n* = 6 in each case). **P* < 0.05 versus control at same time following fracture (analysis of variance)

Conclusion: These data illustrate that routine thromboprophylaxis using LMWH delays osteoprogenitor cell recruitment from the dissociating vascularity. Hence endochondral ossification is significantly attenuated with LMWH therapy. Further studies are mandatory to fully elucidate the effect of these compounds on all aspects of bone turnover and repair.

Effect of adjuvant cyclophosphamide, methotrexate and 5-fluorouracil on Ki67-positive keratinocytes in acute wounds

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Background: Clinicians are often faced with the question of how chemotherapy affects wound healing. The particular cellular events in healing most vulnerable to chemotherapy have not yet been identified. The aim was to quantify these changes during the healing of acute wounds in women with invasive breast cancer.

Methods: In this prospective study, healing was studied in an *in vivo* model. After obtaining full ethics committee approval, patients receiving cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy for breast cancer were biopsied on day 8 of the first treatment cycle. A 3-mm skin punch biopsy was taken from the gluteal region; biopsy was repeated 5 days later. The resulting wound was closed primarily. The control group comprised age-matched patients with breast cancer not receiving CMF or radiotherapy. Serial 6- μ m sections were stained immunohistochemically, using monoclonal antibodies specific for $\alpha_5\beta_1$ integrin, fibronectin and S-phase-associated protein (Ki67). The degree of positive staining was compared using a computerized image analysis programme (Image Pro Plus) and Ki67-positive cells were counted manually.

Results: Fifteen patients were studied (mean age 51 years). Wound re-epithelialization was delayed histologically in patients receiving CMF compared with controls. Using the image analysis software, the level of fibronectin in the provisional matrix was found to be reduced in patients treated with CMF, although no change was observed in the receptor for fibronectin, $\alpha_5\beta_1$ integrin. Data for Ki67-positive keratinocytes adjacent to the wound margin are summarized below.

	Total cells*	Total negative	Total positive	Percentage positive
CMF (n=8)	133(39)	48(29)	85(36)	63.9(21.9)
Control (n=7)	123(29)	24(12)	99(29)	80.5(12.2)†

Values are mean(s.d.). *In four high-power fields. † $P=0.23$ (Mann-Whitney *U* test)

Conclusion: Fibronectin is downregulated within the provisional wound matrix of patients receiving CMF without a similar effect on $\alpha_5\beta_1$ integrin. There is a decrease in the number of Ki67-positive keratinocytes in patients receiving CMF compared with controls. These data may provide useful information to surgeons in the timing of operations in patients receiving chemotherapy.

Distribution of macrophage subpopulation phenotypes in chronic wounds

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Background: Macrophages are thought to play a regulatory role in wound healing. Studies in animal models have shown

that depleting systemic and local populations of macrophages impairs wound closure. It is likely that wound macrophages regulate the various stages of wound healing by secreting an array of messenger molecules at different stages of maturation. Macrophage activity is dependent on differentiation status. Therefore phenotypic subpopulation differences may exist between the wound margin and wound bed of these wounds. The aim of this study was to investigate the possible differences in the subpopulations of macrophages between the wound margin and wound bed of chronic wounds in humans.

Methods: A panel of monoclonal antibodies which identify different macrophage subpopulations was used to stain frozen sections of biopsies taken from the wound margin and bed of ten patients with chronic venous leg ulcers (five in each group). A standard two-stage avidin-biotin peroxidase technique was used. Monoclonal antibodies were selected to stain all macrophages (α -CD68), acute-stage macrophages (27e10, Mac387), primed macrophages (α -mannose receptor; MR) and tissue macrophages (α -sialoadhesin receptor). Neutrophils were identified by staining for non-specific esterase (NSE) activity. The number of positively stained cells was evaluated by counting 12×40 fields sequentially in the margin biopsies and randomly in the bed biopsies.

Results: Macrophages expressing all the differentiation markers were observed in both margin and bed tissues. Wound margin tissue showed a larger number of MR-positive cells (mean(s.e.m.) 45(4)) than the bed (36(2)). Few NSE-positive neutrophils were observed in both, confirming that the staining was restricted to macrophages.

Conclusion: This accumulation of a subpopulation of primed macrophages (MR-positive cells) at the margin-bed interface may be a consequence of an inflammatory response characteristic of healing which is inhibited by an as yet unknown mechanism.

Adjustable handle-shaft needle driver improves endoscopic task performance and reduces wrist flexion and fatigue in the forearm muscles

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Background: At present, endoscopic instruments are designed with the instrument shaft at a fixed angle with the handle. This design imposes an ergonomic restriction that degrades performance and induces muscle fatigue. A novel design handle that enables the surgeon to alter this angle overcomes the problem. It should improve performance and reduce discomfort and muscle fatigue. This study was designed to evaluate endoscopic task performance, motion analysis and electromyography between a conventional fixed angle instrument and a prototype handle that permits alteration of the handle-shaft angle by 15° increments in two axes.

Methods: Ten surgeons of variable laparoscopic experience participated in the study. They sutured in a random sequence 20 enterotomies along the antimesenteric border of porcine

small bowel. Each surgeon sutured two 50-mm enterotomies, one with the handle-shaft angle in the straight (180°) position and the other with the handle-shaft angle adjusted to the surgeon's preference. The endpoints were placement error score, execution time, leaking pressure, motion analysis and telemetric electromyography (integrated muscle work and muscle fatigue) of the dominant upper limb.

Results:

	Straight	Adjustable	P*
Placement error score (mm)	10 (3)	6 (3)	<0.05
Execution time (m)	23.6 (3.4)	20.5 (5.8)	<0.05
Leaking pressure (mmHg)	19.4 (14.6)	27.5 (7.8)	<0.05
Shoulder angle (°)	140 (51)	97 (12)	0.005
Wrist flexion (°)	9 (8)	4 (4)	<0.0001
Forearm flexors			
Integrated work (μv)	4.1 (5.6)	2.4 (1.6)	<0.05
Fatigue angle (°)	16 (9)	26 (20)	0.05

Values are median (interquartile range). *Mann-Whitney test

No significant differences were observed in shoulder angular velocity, elbow angle and angular velocity, and wrist pronation/supination. Surgeons used different handle-shaft angles with the commonest being 15° flexed and 15° inverted.

Conclusion: The adjustable handle driver improves endoscopic performance and motion pattern of the dominant upper limb of surgeons by avoiding awkward forced flexion at the wrist and abduction at the shoulder. It decreases the forearm flexors' muscle work and fatigue, thus enhancing comfort.

Mast cells mediate complement activation following acid aspiration

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Background: A significant role for the alternative complement pathway in acid aspiration has been demonstrated by the observation that C3 but not C4 genetic knockout mice are protected from injury. Using mast cell-deficient WBB6F1J-W/W^V (W/W^V) mice, the hypothesis that mast cells mediate complement activation following acid aspiration was tested. In addition, the mechanism by which mast cells are activated was investigated.

Methods: Tracheostomy tubes were placed in anaesthetized mice and 0.1 normal hydrochloric acid was instilled into the trachea at 2 ml kg⁻¹ following intravenous injection of ¹²⁵I-radiolabelled albumin. After 4 h the ratio of ¹²⁵I-labelled albumin in bronchoalveolar lavage to blood was used to calculate the vascular permeability index (PI). The serum alternative complement pathway, haemolytic activity, was also examined. An identical mouse preparation, except for the omission of radiolabelled albumin, was used for immunohis-

tochemical analysis of complement deposition. Animals were maintained in accordance with National Research Council guidelines.

Results: Sham values were subtracted from each experimental group. PI (mean(s.e.m.)) 0.035(0.002); *n* = 18) in W/W^V mice was 62 per cent less than that of mast cell-sufficient WBB6F1J-+/+ (+/+) animals (PI 0.080(0.005); *n* = 24, *P* < 0.05). A similar reduction (65 per cent) in injury was observed in +/+ mice treated with 15 μg of the chymase inhibitor chymostatin (PI 0.034(0.003); *n* = 16, *P* < 0.05). Treatment of +/+ mice with 10 μg D-Pro2-D-Trp7,9-substance P (DPDT-SP), an antagonist to the neuropeptide substance P, reduced injury by 66 per cent (PI 0.033(0.005); *n* = 15, *P* < 0.05). Serum complement haemolytic activity was intact in W/W^V mice and +/+ animals treated with chymostatin or DPDT-SP, indicating lack of complement activation in these groups, but was reduced to 65 per cent in the untreated +/+ group (*P* < 0.05). In addition, alveolar C3 deposition was intense in untreated +/+ mice but absent in all other groups (*n* = 5 per group).

Conclusion: These observations indicate that mast cells mediate complement activation, probably via the degranulation and release of chymase, following acid aspiration. This mast cell activity appears to be regulated by the release of substance P.

Multicentre randomized controlled trial of nurses and house officers in preoperative assessment

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Background: Preoperative assessment has been criticized for forming too major a component of the work of the preregistration house officer (PRHO). This study assessed whether appropriately trained nurses (ATNs) could perform preoperative assessment to the same standard as PRHOs with comparable cost effectiveness.

Methods: A prospective randomized, controlled, equivalence trial of ATNs and PRHOs was carried out at four sites in three National Health Service Trusts. Consenting patients were randomly allocated to assessment by either an ATN or a PRHO. Competence was determined by a second assessment carried out by one of four specialist registrars in anaesthesia. Three areas of ATN/PRHO performance were judged: history taking, examination and ordering of tests. Each area was graded as correct, overassessed or underassessed and whether an underassessment might have affected perioperative management. The proportion of omissions that may have resulted in a change in perioperative management was compared between the two groups using χ^2 tests.

Results: One thousand nine hundred and twelve patients entered the trial, of whom 1874 were evaluable. Of these, 925

were randomized to the PRHOs and 949 to the ATNs. The ATNs underassessed patients' histories, such as to affect management, in 7 per cent of cases compared with 5 per cent for the PRHOs ($\chi^2 = 0.845$, $P = 0.358$). There was variation in competence between the ATNs, with the ATN on one site performing worse than the PRHOs. An expert panel are reviewing sample records from each study site to determine the extent to which perceived deficiencies in histories are a function of the assessment by the different anaesthetic registrars. In terms of examination, PRHOs and ATNs were equivalent ($\chi^2 = 0.607$, $P = 0.436$). PRHOs and ATNs were equivalent in terms of underordering of tests ($\chi^2 = 0.845$, $P = 0.358$), but PRHOs overordered tests in 21 per cent of cases compared with 12 per cent for ATNs ($\chi^2 = 35.364$, $P < 0.0001$). Overordering of tests was not related to the severity of the cases as judged by American Society of Anesthesiologists rating.

Conclusion: The quality of preoperative assessment achieved by ATNs is comparable to that of PRHOs. Further work is in progress on the economic implications of test overordering. Implementation of the recommendations from this study will have a significant impact in helping to facilitate the reduction in junior doctors' hours.

Assessment of laparoscopic skill in basic surgical trainees

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Background: There has been recent interest in the use of simulation to objectively assess the operating skill of surgical trainees. There is little evidence that performance on currently available laparoscopic simulators correlates with actual technical ability. Trainee performance has been compared on two laparoscopic simulators with (1) consultant technical skill assessment and (2) performance of controls with no experience of laparoscopic surgery.

Methods: Laparoscopic assessment was carried out on 30 basic surgical trainees and 37 first-year medical students. Error rate, economy of movement and time taken for each subject to complete two tasks on MIST-VR (minimally invasive surgical trainer-virtual reality; Ethskills, UK) and a conventional box trainer (Ethskills) were recorded. A 19-point technical skill assessment form, based on direct observation of trainee performance in the operating theatre, was also completed by each trainee's supervising consultant. Spearman's rank correlation was used to test for relationships between the three trainee assessment methods, and between each method and duration of surgical experience. Mann-Whitney test was used to test for differences in performance between basic surgical trainees and medical students.

Results: There was a positive correlation between time and error for tasks on both trainers (conventional: $\rho = 0.578$, $P = 0.001$; MIST-VR: $\rho = 0.368$, $P = 0.045$) and between time and economy for tasks on MIST-VR ($\rho = 0.747$, $P = 0.001$).

Time and error on the conventional simulator correlated with that on the MIST-VR ($\rho = 0.510$, $P = 0.004$ and $\rho = 0.538$, $P = 0.002$ respectively). Consultant assessment correlated positively with duration of surgical experience ($\rho = 0.564$, $P = 0.001$). No significant correlation was found between laparoscopic simulator performance and either consultant assessment or duration of surgical experience. There was also no significant difference between trainees and medical students in performance on either laparoscopic simulator.

Conclusion: Performance of basic surgical trainees on laparoscopic simulators does not appear to correlate with actual technical ability, as measured by both consultant technical skill assessment and duration of surgical experience, and is no better than the performance of medical students. Further work is needed before such simulators are used for formal assessment of technical skill.

Experimental study of the effects of tamoxifen on wound contraction and granulation tissue in excisional wounds

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Background: In the fibroproliferative disorders Dupuytren's contracture, Peyronie's disease and desmoid tumour, myofibroblasts (the cells responsible for wound contraction) have a central role. Regression of these disorders has been reported with tamoxifen, although the mechanism is unknown. The effects of tamoxifen on wound contraction and granulation tissue were therefore investigated in the rat.

Methods: With Home Office approval, 60 adult Hooded Lister rats were given $15 \times 15 \text{ mm}^2$ dorsal excisional wounds under general anaesthesia, and then randomized into ten groups to receive, by gavage, 1 ml kg^{-1} water (controls) or tamoxifen (0.03 , 0.1 , 0.3 and 1.0 mg kg^{-1}) for 5 or 10 days. The wounds were traced daily and digitized and the coefficients of wound contraction (gradient of plot $\log/\text{area}$ versus time) calculated. The wounds were then excised; half for analysis by histology, immunostaining (anti- α -1 actin) and electron microscopy, and the other half for investigation of *in vitro* contractility responses to the myofibroblast stimulant mepyramine. Statistical analysis was by Wilcoxon signed rank test.

Results: Results are expressed as mean(s.d.). Contraction rates were increased for days 0–5 in the groups treated at doses of 0.03 mg kg^{-1} ($-0.088(0.019)$ versus $-0.076(0.019)$ for controls; $P < 0.05$) and 0.1 mg kg^{-1} ($-0.090(0.030)$; $P < 0.05$); and for days 2–10 at doses of 0.03 mg kg^{-1} ($-0.096(0.014)$ versus $-0.072(0.010)$; $P < 0.05$), 0.1 mg kg^{-1} ($-0.103(0.023)$; $P < 0.05$) and 0.3 mg kg^{-1} ($-0.097(0.020)$; $P < 0.05$). Granulation tissue contractility was enhanced in the same treated groups at day 10, as follows: controls, $2.716(0.848) \text{ mg kg}^{-1}$; 0.03 mg kg^{-1} , $4.495(1.201) \text{ mg kg}^{-1}$ ($P < 0.05$); 0.1 mg kg^{-1} , $4.217(1.010) \text{ mg kg}^{-1}$ ($P < 0.05$); and 0.3 mg kg^{-1} , $4.540(1.690) \text{ mg kg}^{-1}$ ($P < 0.05$).

($P < 0.05$). These quantitative differences were reflected by qualitative changes in the histological, immunohistological and electron microscopic appearances.

Conclusion: Tamoxifen alters *in vivo* wound contraction, with concomitant effects on structure, ultrastructure and *in vitro* contractility of the wound granulation tissue.

Reliability and validity of endoscopic tester for assessment of single-hand performance

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Background: A computer-controlled endoscopic tester has been designed for standard objective assessment of single-hand performance. The system utilizes standard video-endoscopic equipment. The target consists of two plates with 37 holes in the front plate. Each run consists of passing a probe through the centre of each hole in a random sequence. The system measures the force applied on the back plate and horizontal and vertical angular deviations of the probe in relation to the centre of the selected hole. An error is registered when the probe touches the hole rim or the task exceeds the allocation time. The aim of the study was to evaluate the reliability and the concurrent validity of the endoscopic tester against standard psychological tests.

Methods: Twenty medical students performed two familiarization and five test runs on the endoscopic tester using the dominant hand. Subjects were also tested on four psychological tests: the space relations and abstract reasoning of differential aptitude test, the embedded figures test and the Crawford small parts dexterity test. The outcome measures of the endoscopic tester were standardized scores of number of successful tasks per run, force, execution time and angular deviations. An endoscopic manipulation score was constructed from execution time, force and angular deviations to facilitate the correlation with psychological tests. High manipulation score indicates poor performance on the system. Analysis of variance, coefficient alpha and Pearson product correlation were used for statistical analysis.

Results: Internal consistency of the system was shown by the high coefficient alpha ($r > 0.7$) between the outcome measures. Angular deviations and execution time improved with practice ($P < 0.05$), while force and number of successful tasks did not ($P > 0.1$). There was a significant difference between subjects in all outcome measures ($P < 0.0001$). The endoscopic manipulation score correlated negatively with the space relations and the abstract reasoning tests ($r = -0.6$), which measure visuospatial ability.

Conclusion: This study confirmed the reliability of the endoscopic tester. The performance on the endoscopic system correlates with visuospatial psychological testing. Some parameters of endoscopic performance improve with practice, highlighting the effect of training, while others do not, reflecting innate abilities.

Detection of free malignant cells in the peritoneal cavity using magnetic activated cell sorting

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Background: The presence of residual cancer cells in the peritoneal cavity after colorectal surgery is thought to increase the risk of local recurrence. Epithelial cancer cells express human epithelial antigen (HEA), enabling their detection by an immunomagnetic cell enrichment technique.

Methods: Standardized peritoneal washings were performed on a number of patients ($n = 23$) undergoing colorectal cancer surgery before and after cancer resection. Malignant and mononuclear cells were isolated from the washings by centrifugation over a density gradient medium and incubated with magnetic microbeads bound to HEA antibody. Cancer cells were harvested by passage through a magnetic field and subjected to cytological examination.

Results: Overall 13 of 23 patients had positive cytology. Five of 23 had low numbers of cancer cells present in the preresection lavage and 11 patients had cancer cells present after resection. In nine of the 11 positive postresection samples there was a more than tenfold increase in the number of cancer cells present.

Conclusion: The presence of free malignant cells in the peritoneal cavity may have implications for surgical technique and the need for adjuvant therapy.

Probiotic therapy stabilizes the gut mucosal barrier in the interleukin 10 knockout model of colitis

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Background: Inflammatory bowel disease is characterized by inflammatory cell infiltration, increased intestinal permeability and disturbed bacterial flora. Studies with knockout mice have shown a crucial role for colonic bacteria in the pathogenesis of colitis. These observations have led to the hypothesis that increasing the number of protective colonic bacteria may ameliorate colitis. The present study investigated this hypothesis by assessing the effect of *Lactobacillus plantarum* sp. 299 (LP299) on intestinal inflammation, permeability and endotoxaemia in the interleukin 10 knockout mouse model of colitis.

Methods: Animals were bred and weaned in specific pathogen-free conditions before transfer to a conventional environment at 4 weeks of age. Untreated animals were evaluated at 6, 12 and 15 weeks of age. Animals in the treatment arms received either 10^{10} colony forming units of LP299 in oat fibre solution or a sterile oat fibre solution (placebo) daily by gavage from 6 weeks of age to either 12 or 15 weeks. Twenty-four hours before

completion of the experiment, all mice received radiolabelled polyethylene glycol by gavage and were housed in a metabolic cage. Urine was collected for 24 h to assess gut permeability. Animals were anaesthetized and blood taken by cardiac puncture for antiendotoxin core antibody (EndoCAB) measurement by enzyme-linked immunoabsorbent assay. Colons were harvested for histological inflammation scoring (HIS).

Results:

Groups	Age (weeks)	n	HIS	Permeability	EndoCAB IgG
Untreated	6	6	0.33(0.21)	0.22(0.05)	75.6(2.2)
Untreated	12	6	7.16(1.19)	0.76(0.31)	91.6(4.9)
LP299	6–12	10	2.90(0.05)*†	0.10(0.02)*†	70.8(2.5)*
Placebo	6–12	9	5.33(1.05)	0.36(0.05)*	72.3(3.4)*

Values are mean(s.e.m.). Ig, immunoglobulin. * $P < 0.05$ versus untreated 12-week-old animals. † $P < 0.05$ versus placebo group

A similar pattern was observed in animals treated to 15 weeks.

Conclusion: LP299 reduces the severity of colitis with a corresponding decrease in gut permeability and IgG EndoCAB concentration. These results indicate that LP299 stabilizes the gut mucosal barrier in this model.

Randomized trial of circular stapling procedure for haemorrhoids versus Milligan–Morgan haemorrhoidectomy

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Background: The use of a circular transanal stapling technique for the treatment of haemorrhoids has been described but has not been subjected to randomized controlled trial.

Methods: Following local ethics committee approval, a randomized controlled trial was performed. Forty consecutive patients admitted for surgical treatment of prolapsing haemorrhoids were assigned randomly to Milligan–Morgan haemorrhoidectomy ($n = 20$) or the circular stapled procedure. Under general anaesthesia, patients underwent standardized diathermy excision haemorrhoidectomy after Milligan–Morgan or had a circumferential doughnut of rectal mucosa and submucosa above the dentate line excised and closed with a standard circular end-to-end stapling device. Patients completed linear analogue pain charts each day, and were interviewed at 1 and 3 weeks and 3 months after operation.

Results: The stapled group had a significantly shorter anaesthesia time (median 18 (range 9–25) versus 22 (range 15–35) min; $P = 0.007$, Mann–Whitney U test). Pain scores were significantly less in the stapled group from day 1 after operation and were most different on day 7 (median linear analogue pain score 1.1 (range 0–6.8) cm for stapled versus 5.8 (range 1.4–10) cm for open group; 95 per cent confidence interval for difference in medians 1.5–6.7 cm; $P = 0.0007$, Mann–Whitney U test). Expected pain was also significantly less in the stapled

group commencing day 1 onwards and was most significantly different on day 6 (median linear analogue expected pain score (scale –5 (enormously better) to +5 (far worse)) –4.4 (range –5 to +3.3) cm for stapled versus +1.2 (range –4.2 to +4.8) cm for open group; 95 per cent confidence interval of difference in medians 2.3–5 cm; $P = 0.0007$, Mann–Whitney U test). Hospital stay and time to first bowel motion were not significantly different between groups. Return to normal activity was significantly shorter in the stapled group (median 17 (range 3–60) versus 34 (range 14–90) days; $P = 0.0002$, Mann–Whitney U test). Over median follow-up of 125 (range 77–206) days, satisfaction with symptom control was similar in both groups; 85 per cent of patients in the stapled group and 75 per cent in the Milligan–Morgan group rated their symptom control as excellent or good.

Conclusion: The circular stapled technique for haemorrhoids offers a significantly less painful alternative to Milligan–Morgan haemorrhoidectomy and is associated with an earlier return to normal activity. Early symptom control and functional outcome appear comparable but longer-term symptomatic and functional outcomes require further study.

Puborectalis plays an important part in the generation of squeeze pressure in normal adults

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Background: Anal canal squeeze pressure is assumed to result from external sphincter contraction, but the contribution from other muscles has not been explored.

Methods: Ten male and ten nulliparous female asymptomatic subjects underwent three-dimensional anal endosonography and manometry. Incremental squeeze pressures at 0.5-cm intervals, expressed as a percentage of the maximum recorded, were related to the following anatomical levels: puborectalis, overlap between external anal sphincter and puborectalis, external and internal anal sphincter, and external anal sphincter only. These levels were determined by coronal and sagittal endosonographic reconstructions. Statistical testing was by Mann–Whitney U test.

Results: The length of puborectalis was not significantly different between men and women (median 23.9 versus 27.1 mm) but it represented a greater proportion of the anal canal length in women (61 versus 45 per cent; $P = 0.02$). In men puborectalis was associated with 71 (range 32–100) per cent and in women with 62 (range 32–100) per cent of the maximum squeeze, compared with 91 (range 52–100) and 94 (52–100) per cent respectively for the external sphincter. There was no significant difference in percentage maximum pressures between men and women at any of the anatomical levels. The percentage of maximum pressure at puborectalis level was

Anatomical level	Percentage of maximum squeeze
Rectum	12 (0–39)
Puborectalis	62 (32–100)
Puborectalis and external sphincter	93 (47–100)
External with internal sphincter	91 (51–100)
External sphincter alone	65 (4–100)

Values are median (range) for both sexes

significantly lower than at the levels of either external with internal sphincter ($P < 0.01$) or puborectalis and external sphincter ($P = 0.06$), but no different from that of the external sphincter alone ($P = 0.91$).

Conclusion: The muscular components of the anal canal contribute to squeeze pressure to the same extent in men and women. Maximal canal squeeze is found where the puborectalis overlaps the external sphincter. The squeeze pressure at the level of puborectalis is similar to that at the external sphincter below the termination of the internal sphincter. This segment represents a significant proportion of anal canal length in women.

Microflora differ in ileal pouches for ulcerative colitis and familial polyposis coli

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Background: Alterations in ileal pouch bacterial flora have been implicated in the pathogenesis of pouchitis, which occurs in patients with ileal pouches created for ulcerative colitis (UC) but not for familial adenomatous polyposis (FAP). Microbial studies have not identified a specific pathogen to account for pouchitis. The presence of sulphate reducing bacteria (SRB) has recently been implicated in the aetiology of UC. SRB produce hydrogen sulphide, which results in crypt architectural distortion and ulceration following colonic mucosal exposure. The aim of this study was to determine if there are differences between bacterial populations in patients with ileal pouches constructed for UC or FAP.

Methods: Faecal samples were taken from ten patients with an ileal pouch for UC, from seven patients with an ileal pouch for FAP and from eight patients with an ileostomy but no pouch for UC. Microbial analysis of faeces was performed for each patient to enumerate populations of *Lactobacillus*, *Bifidobacteria*, *Bacteroides*, *Clostridium perfringens*, enterococci and coliforms. SRB were enumerated following a 2-week incubation in modified Postgate medium using the most probable number technique.

Results: Eight of the ten patients with an ileal pouch for UC harboured SRB. In contrast, SRB were not detected in any

patient with an ileal pouch for FAP. As expected none of the patients with an ileostomy but no pouch for UC harboured SRB. There was no significant difference in populations of *Lactobacillus*, *Bifidobacteria*, *Bacteroides*, *Clostridium perfringens*, enterococci or coliforms between UC ileal pouches and FAP ileal pouches.

Conclusion: SRB activity is a feature of ileal pouches constructed in patients who have UC but not FAP. This finding may reflect genetic differences in the host.

Dietary *n*-3 essential fatty acids modulate cytokine production in patients with ulcerative colitis

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Background: The aetiology of ulcerative colitis is unclear, but one hypothesis is that there is an increase in immune activity resulting in tissue damage. Dietary supplementation with *n*-3 essential fatty acids (EFAs) has been shown to result in a symptomatic improvement in patients with ulcerative colitis and suppression of systemic natural cytotoxicity. The reasons for this are unclear. Interest has focused on the immunoregulatory roles of key cytokines such as interleukin (IL) 8, which is a proinflammatory mediator, and IL-10, which suppresses cellular immunity. The aim of this study was to determine the effects of supplementation with *n*-3 EFAs on systemic and gut cytokine production in patients with ulcerative colitis.

Methods: Patients with active ulcerative colitis ($n = 30$), receiving standard therapy, were randomized to receive dietary supplementation with *n*-3 EFAs (eicosapentaenoic acid 3.2 g day^{-1} and docosahexaenoic acid 2.4 g day^{-1}) or placebo (sunflower oil) for 6 months. The levels of a range of cytokines in colonic washouts and serum were measured before commencement of therapy, 3 months later and after 6 months.

Results: Results are presented as median (interquartile range). After 6 months there was a reduction in the serum concentration of IL-8 in patients receiving *n*-3 EFAs to $22.9 (12.3-137.6) \text{ pg ml}^{-1}$ compared with $81.1 (38.7-130.3) \text{ pg ml}^{-1}$ in patients in the placebo group ($P < 0.05$). In contrast, there was an increase in IL-10 in patients taking *n*-3 EFAs ($6.6 (1.5-28.4) \text{ pg ml}^{-1}$) compared with those in the placebo group ($81.1 (1.1-5.3) \text{ pg ml}^{-1}$) ($P < 0.05$). There were no significant differences in levels of IL-1 α , IL-1 β , IL-2, IL-6, IL-12, IL-15 or γ -interferon. While levels of IL-8 and IL-10 in the colonic washout demonstrated a similar trend, this was not significant.

Conclusion: This pilot study has demonstrated a reduction in IL-8 production and an increase in IL-10 production by *n*-3 EFAs, which may explain the symptomatic improvement in patients with extensive ulcerative colitis.

Regulation of prostaglandin $F_{2\alpha}$ -induced chloride secretion in human colon

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Background: Infective and inflammatory insults generate chloride secretion induced by endogenous mediators or exogenous toxins. Sodium and water follow down electrochemical and osmotic gradients to cause diarrhoea. Prostanoids mediate varied functions from growth regulation to inflammation in the human colon. The effects of a putative secretagogue prostaglandin (PG) $F_{2\alpha}$ on human colon were investigated.

Methods: Mucosal epithelium from colectomy specimens was mounted in Ussing chambers. Chloride secretion was quantified as changes in short circuit current (I_{SC}). Cellular adenosine 3',5'-cyclic monophosphate (cAMP) levels were measured by radioimmunoassay. Crypts were isolated by calcium chelation, and intracellular pH (pH_i) was measured by 2',7'-bis(2-carboxy-ethyl)-5,6-carboxyfluorescein spectrofluorescence imaging. Sodium-hydrogen exchange (NHE1) was inhibited with ethylisopropylamiloride $10 \mu\text{mol l}^{-1}$. Results are expressed as mean (s.e.m.) ($n=8$) at $\text{PGF}_{2\alpha}$ 100 nmol l^{-1} in each case. Statistical analysis was by Mann-Whitney U test.

Results: $\text{PGF}_{2\alpha}$ increased cellular cAMP ($32.7(3.4) \text{ pmol mg}^{-1}$; $P<0.05$) and induced a cytosolic acidification (pH_i fell from $7.21(0.06)$ to $7.04(0.01)$; $P<0.01$) at 10 min. This acidification did not occur following inhibition of NHE1 ($P<0.01$). $\text{PGF}_{2\alpha}$ induced chloride secretion (I_{SC} $54.6(12.4) \mu\text{A cm}^{-2}$; $P<0.01$) that was reduced by inhibition of sodium-potassium-chloride cotransport (NKCC) with bumetanide $100 \mu\text{mol l}^{-1}$ (I_{SC} $18.1(8.3) \mu\text{A cm}^{-2}$; $P<0.01$). Blockade of serosal calcium-regulated potassium channels inhibited chloride secretion (I_{SC} $3.6(1.8) \mu\text{A cm}^{-2}$; $P<0.01$).

Conclusion: $\text{PGF}_{2\alpha}$ generates cAMP-mediated chloride secretion in the human colon. The electrochemical driving force for secretion is maintained by serosal membrane NKCC and potassium channels. These potassium channels are targets for intervention in hypersecretory states. The intracellular acidosis induced by $\text{PGF}_{2\alpha}$ may be due to an inhibition of NHE1 activity. This finding has implications for the regulation of ion transport, mitogenesis and apoptosis.

Effect of indoramin and salbutamol on anal canal pressure

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Background: Internal anal sphincter tone is dependent on the intrinsic myogenic properties of smooth muscle and on external neural influences, specifically a continuous sympa-

thetic input. Reduction of maximum resting anal canal pressure (MRP) increases the vascularity of ischaemic chronic anal fissures and promotes healing.

Methods: Ten patients with chronic anal fissures (median age 36 (range 28–65) years; six women) and ten healthy volunteers (median age 28 (range 21–38) years; five women) were administered either indoramin 20 mg (α_1 antagonist) or salbutamol 4 mg (β_2 agonist) orally in a double-blinded manner. MRP, pulse and blood pressure were measured before and at hourly intervals until 3 h after administration of oral agent.

Results: Patients with chronic anal fissures had a significantly higher MRP than volunteers ($P<0.05$; Mann-Whitney U test).

	Patients with anal fissures		Healthy volunteers	
	Indoramin	Salbutamol	Indoramin	Salbutamol
Resting MRP (cmH ₂ O)	147.0(44.4)	144.5(37.6)	87.4(32.0)	101.1(34.6)
MRP reduction (at 3 h) (cmH ₂ O)	60.9(29.2)	48.0(28.7)	28.1(22.8)	34.8(23.7)
% MRP reduction (at 3 h) (cmH ₂ O)	40.4(9.8)	32.9(19.0)	29.3(23.2)	31.6(19.0)

Values are mean (s.d.)

In each group there was a significant reduction in MRP at 1, 2 and 3 h ($P<0.05$; Wilcoxon signed rank test). There was no significant difference between indoramin and salbutamol in terms of reduction of MRP in patients and volunteers (Mann-Whitney U test). The reduction in patients' MRP at 3 h was comparable to that after lateral sphincterotomy. Tremors were noted with salbutamol in four volunteers and five patients. Three patients complained of light-headedness with indoramin without a significant change in diastolic blood pressure. The reduction in MRP in subjects who took indoramin did not correlate with a reduction in diastolic blood pressure (Pearson correlation coefficient $r=0.166$, P not significant).

Conclusion: Oral indoramin causes a sustained reduction in MRP without serious side-effects and may have a beneficial role in the treatment of anal fissure.

Matrix metalloproteinase activity in colorectal cancer

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Background: Matrix metalloproteinases (MMPs) are involved in extracellular matrix (ECM) degradation at several stages of the metastatic cascade. It is the balance between the expression of active MMPs and their tissue inhibitors (TIMPs) that determines ECM degradation *in vivo*. This study compared MMP and TIMP expression and total MMP activity in paired colorectal tumour and normal tissue ($n=50$) and correlated their expression to clinical pathological staging.

Methods: Fresh tissue samples were collected and analysed by gelatin zymography (MMP-2 and MMP-9 expression), enzyme-linked immunosorbent assay (MMP-1, MMP-3, TIMP-1 and TIMP-2) and quenched fluorescence substrate hydrolysis (total MMP activity). Statistical analysis was by Mann-Whitney and Spearman's correlation.

Results: The expression of the active forms of MMP-2 and MMP-9 was significantly greater in tumours than in normal colon (MMP-2: 98 per cent of tumours, 52 per cent of normal samples; MMP-9: 92 per cent of tumours, 8 per cent of normal samples). MMP-1, MMP-3 and TIMP-1 expression were significantly greater in tumour tissue (TIMP-1: tumour median 72 (range 25–351) ng mg total protein⁻¹; normal 26 (range 4–107) ng mg⁻¹). TIMP-2 expression was significantly greater in normal tissue. The total MMP activity was also significantly greater in tumours: 14 750 (range 1750–174 400) *versus* 7250 (range 750–354 650) pmol min⁻¹ mg protein⁻¹. MMP-1 and TIMP-1 expression correlated significantly with both Dukes stage (MMP-1: adenomas 0.8 (0.2–3.6); Dukes A 3.9 (0.1–21.0); Dukes 'D' 23.5 (16.3–30.8)), differentiation and lymphatic invasion (MMP-1: lymphatic invasion 16.3 (0.9–52.1); no invasion 5.7 (0.1–32.3)). Total MMP activity correlated with the tumour size.

Conclusion: The expression of individual MMPs and total MMP activity was upregulated in colorectal tumour tissue compared with normal, which may lead to increased ECM degradation *in vivo*.

Pathophysiological study of the effects of floppy Nissen fundoplication and the influence of crural repair and fundal mobilization

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Background: Although floppy Nissen fundoplication (FNF) is an effective antireflux procedure, patient satisfaction is frequently compromised by mechanical complications including dysphagia, gas bloat and inability to belch or vomit. Studies have suggested that FNF produces a supracompetent high-pressure zone with impaired relaxation on swallowing. Fundal mobilization has been advocated as a means of reducing this problem but reports of the efficacy of this manoeuvre are conflicting and the role of crural repair is controversial.

Methods: The rabbit cardiomyectomy reflux model was used to perform FNF. Home Office and ethics committee approval were obtained. Manometric lower oesophageal sphincter (LOS) characteristics including resting pressure (LOSP) and nadir relaxation pressure, together with intraoesophageal pH profile, were studied before and 1 month after operation in 24 animals undergoing FNF with and without crural repair and short gastric vessel (SGV) division. Before the animals were killed, intragastric bursting pressure and gastric volume to overcome the antireflux mechanism were measured.

Results: Reflux was controlled in 96 per cent of animals with an overall mean increase in LOSP of 56 per cent and mean nadir relaxation pressure of 4.8 mmHg. The addition of crural repair did not influence competence and had a small effect on mean gastric bursting pressure (22.0 *versus* 19.8 mmHg; *P* not significant) and bursting volume (222 *versus* 208 ml; *P* not significant). Crural repair was associated with a greater increase in LOSP (76.9 *versus* 34.5 mmHg; *P* < 0.001) and a higher nadir relaxation pressure (6.6 *versus* 3.0 mmHg; *P* < 0.001). SGV division resulted in a smaller increase in LOSP (54.2 *versus* 14.7 mmHg; *P* < 0.001) in the absence of crural repair only and no change in nadir relaxation pressure whether or not crural repair was performed (6.2 *versus* 7.0 mmHg, *P* not significant; 2.88 *versus* 3.03 mmHg, *P* not significant).

Conclusion: FNF effectively controlled reflux, which was associated with a significant increase in resting LOSP and impairment of LOS relaxation. Competence was similar whether or not crural repair was performed, although crural repair resulted in greater impairment of relaxation. Fundal mobilization resulted in a smaller increase in resting LOSP and a lower nadir relaxation pressure in the absence of crural repair but made no difference when crural repair was performed.

Symptoms and physiology fail to predict global quality of life before and after antireflux surgery

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Background: Laparoscopic surgery has led to an increase in the number of patients being offered a surgical solution to gastro-oesophageal reflux disease (GORD). This surgery is aimed purely at improving quality of life (QoL) rather than prolonging life. The EuroQol (EQ-5D) questionnaire is a standardized generic tool for describing health-related QoL. It measures five dimensions at three levels and allows generation of global QoL scores using time trade off (TTO) data and a visual analogue scale (VAS). The aim of this study was to assess whether physiological measurement or reflux symptom scoring could predict overall QoL before and after laparoscopic antireflux surgery.

Methods: Some 43 patients underwent preoperative and postoperative (between 6 and 12 months) oesophageal manometric and pH studies, which permitted calculation of a composite acid reflux (DeMeester) score. Patients also completed a reflux-related symptom (modified DeMeester) questionnaire, which generated a modified DeMeester score (range 0–9), and an EQ-5D questionnaire before and 12 months after operation.

Results: The Table shows Spearman rank correlation coefficients relating to clinical measures of GORD and scores in the EuroQol questionnaire.

	Before operation		After operation	
	VAS	TTO	VAS	TTO
LOS pressure	-0.054	-0.128	-0.149	-0.382
DeMeester score	0.323	0.111	-0.109	-0.144
Modified DeMeester score	-0.316	-0.208	0.296	0.224

Conclusion: There was no correlation between either of the global measures of QoL and the preoperative or postoperative quantitative pathophysiological measures or the symptom score performed. This supports the independent assessment of QoL in patients with GORD who are to be considered for antireflux surgery in order to fully assess the effect of surgery on their QoL.

Urinary trypsinogen activation peptide is a reliable early predictor of severity in acute pancreatitis

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Background: There is an urgent need for a reliable early prognostic marker in acute pancreatitis. The results of a prospective multicentre study, comparing a new competitive immunoassay for trypsinogen activation peptide (TAP) with three standard clinicobiochemical scoring systems and with C-reactive protein (CRP) levels, are reported.

Methods: One hundred and seventy-two patients with acute pancreatitis were recruited, of whom 35 had severe disease as defined by the Atlanta criteria. Seventy-four patients with acute abdominal pain of other causes served as controls. TAP levels were measured in urine samples taken on admission and at 12, 24, 36, 48, 72, 96 and 168 h thereafter (Tapkit; Biotrin International, Dublin, Ireland).

Results: Urinary TAP peaked 12 h after symptom onset at mean (s.e.m.) $111(45)\text{ nmol l}^{-1}$ in those with severe disease compared with $36(11)\text{ nmol l}^{-1}$ for mild disease and $20(7)\text{ nmol l}^{-1}$ for controls ($P < 0.05$). Urinary TAP levels greater than 35 nmol l^{-1} within 24 h of symptom onset differentiated severe from mild disease with sensitivity, specificity and negative predictive values (NPV) of 58, 73 and 86 per cent respectively. These results compared with zero, 50 and 75 per cent for CRP concentration greater than 150 mg l^{-1} . At 24 h after symptom onset the area (95 per cent confidence interval) under the receiver operator characteristic curve was greater for TAP (0.69 (0.51–0.88)) than for CRP (0.40 (0.23–0.58)). Urinary TAP levels remained consistently higher in patients with severe acute pancreatitis up to 84 h after the onset of symptoms. At 48 h after hospitalization the sensitivity, specificity and NPV for a TAP concentration greater than

35 nmol l^{-1} were 83, 72 and 94 per cent; compared with 86, 61 and 94 per cent for a CRP concentration greater than 150 mg l^{-1} ; 56, 64 and 85 per cent for an Acute Physiology And Chronic Health Evaluation II score above 8; 89, 64 and 96 per cent for Ranson 3; and 77, 75 and 93 per cent for Imrie (3).

Conclusion: Urinary TAP is at least as good a predictor of severity as any of the currently utilized scoring systems, but its simplicity and applicability within 12 h of symptom onset make it an extremely valuable severity marker in the assessment of patients with acute pancreatitis.

Carboxypeptidase B activation peptide and L-selectin as severity markers in acute pancreatitis

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Background: Acute pancreatitis is a common surgical emergency of unpredictable course. To date an optimal severity marker in acute pancreatitis is still lacking. Carboxypeptidase B (CAPAP-B) concentration correlates with the activation of trypsinogen which is involved in the pathogenesis of acute pancreatitis. L-selectin is a product of leucocyte activation and may play a central role in the pathogenesis of acute inflammation. This study aimed to assess immunoreactive CAPAP-B (irCAPAP-B) in serum and urine, and L-selectin in serum as severity markers in acute pancreatitis on admission. The accuracy of these markers was compared with Acute Physiology And Chronic Health Evaluation II score and C-reactive protein (CRP) levels in predicting severe acute pancreatitis.

Methods: This prospective study included 71 individuals (23 patients with acute pancreatitis, 20 controls with non-pancreatic acute abdomen and 28 age- and sex-matched healthy volunteers). Severity classification was based on Atlanta criteria. Levels of irCAPAP-B were measured in serum and urine for all patients on admission by radioimmunoassay. L-selectin was measured in serum by enzyme-linked immunosorbent assay. APACHE II scores and CRP levels were also assessed in subjects with acute pancreatitis and acute abdomen. The Mann-Whitney *U* test and receiver operating characteristic curve were used to analyse the results statistically.

Results:

	Mild	Severe	Controls	Volunteers
Serum irCAPAP-B (nmol l^{-1})	2.4 (0.3–6.5)*	7.2 (6.3–17.3)	0.7 (0.5–2.5)*	1.1 (0.6–1.4)*
Urine irCAPAP-B (nmol l^{-1})	11.5 (2.4–6.8)*	134.4 (35–46.9)	8.5 (3.1–50.2)*	8.6 (3.7–11.1)*
Serum L-selectin (ng ml^{-1})	558 (294–999)	537 (301–800)	446 (435–735)*	1257 (575–1911)*
APACHE II	4 (0–11)*	9 (5–11)	3 (0–13)	
CRP (mg l^{-1})	35 (6–832)	17 (12–292)	242 (76–250)	

Values are median (interquartile range) * $P < 0.05$ versus severe

The sensitivity and specificity, respectively, for values on admission were 100 and 87 per cent for serum irCAPAP-B (cut-off greater than 6 nmol l^{-1}), 100 and 94 per cent for urinary irCAPAP-B (cut-off greater than 30 nmol l^{-1}), 71 and 75 per cent for APACHE II score (cut-off greater than 5), and 50 and 39 per cent for CRP (cut-off greater than 20 mg l^{-1}).

Conclusion: Serum and urinary levels of irCAPAP-B were significantly higher in patients with severe acute pancreatitis. On admission, both were more sensitive and specific than APACHE II and CRP as severity markers. Serum L-selectin did not predict disease severity.

Gastric mucosal irradiation with a carbon dioxide laser promotes healing in a model of peptic ulceration

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Background: Current antiulcer treatment emphasizes the use of pharmacological agents. Defocused carbon dioxide laser (wavelength $10\,600 \text{ nm}$) produces a very superficial thermal effect on gastric mucosa and has been shown to reduce gastric acid secretion. This study assessed the use of defocused carbon dioxide laser therapy to heal ulcers in an experimental model of peptic ulcer disease.

Methods: Sprague-Dawley rats were randomized into two groups (1 and 2), both with peptic ulceration induced by cysteamine gavage at 750 mg kg^{-1} . Both groups were weighed and had a gastrotomy on day 5. An ulcer index was calculated from the product of the total number of ulcers and the sum of the ulcer length. Ulcer severity was graded on a scale of 0–4 (0, no ulcers; 1, superficial erosions; 2, linear ulcers; 3, haemorrhagic ulcers; 4, perforated ulcers). The laser-treated group (group 2) received mucosal irradiation with a defocused carbon dioxide laser at 5 W with a spot beam size of 1 cm. Four weeks later the animals were weighed and the stomachs were examined for ulcer index and severity.

Results:

	Mean ulcer index		Mean ulcer grade	
	Before treatment	After treatment	Before treatment	After treatment
Group 1 ($n=12$)	8.6(2.1)	8.2(2.2)	1.9(0.1)	2.6(0.2)
Group 2 ($n=15$)	8.7(1.5)	1.3(0.5)	1.8(0.1)	1.7(0.2)*

Values are mean(s.e.m.). * $P < 0.05$ versus group 1 (Kruskal–Wallis test)

Treatment with the defocused carbon dioxide laser significantly reduced ulcer index and ulcer grade. Untreated animals also demonstrated weight loss (mean 0.5 g) compared with weight gain in the treatment group (mean 3.3 g).

Conclusion: The defocused carbon dioxide laser successfully healed ulcers in this model of peptic ulcer disease. This therapy

could be administered endoscopically and has the potential benefit of being a one-stop treatment strategy.

Expression of cell cycle regulatory and microtubule stabilization genes in oesophageal adenocarcinomas

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Background: The cell cycle regulatory protein kinase, cell division cycle (CDC) 2, is activated by CDC25-induced dephosphorylation. Overexpression of CDC25 causes upregulation of CDC2 which not only drives mitosis into a hyperproliferative state but also phosphorylates the microtubule stabilization protein, microtubule-associated protein tau (MAPT) into a dysfunctional form, leading to abnormal cellular morphology. CDC25 is overexpressed in lung, gastric and head and neck cancers, while downregulation of MAPT has not previously been implicated in carcinogenesis. Derangement of both may predispose to malignant potential. This study aimed to examine the expression of the cell cycle regulatory genes *CDC25* (forms A and B) and *CDC2* and concomitant expression of MAPT in oesophageal adenocarcinomas.

Methods: RNA and genomic DNA was extracted from matched normal and malignant mucosa from 18 patients with oesophageal adenocarcinomas. Using semiquantitative reverse transcriptase–polymerase chain reaction (RT–PCR), levels of gene expression were visualized by gel electrophoresis. Comparative genomic hybridization (CGH) was used to identify regions of gene amplification and gene deletion on tumour DNA from four primary cancers and one oesophageal adenocarcinoma cell line, and matched to normal reference DNA.

Results: By RT–PCR analysis, 17 of 18 tumours showed overexpression of either A or B isoforms of CDC25 and 12 showed overexpression of CDC2. MAPT was downregulated in 13 of the 17 tumours. Of nine tumours expressing high levels of both CDC25A and CDC25B, all demonstrated marked expression of CDC2 and concomitant loss of MAPT with 100 per cent concordance. To corroborate this finding, CGH revealed a region of gene amplification encompassing the locus for CDC25B on chromosome 20p and a region of loss surrounding the locus for MAPT on chromosome 17q.

Conclusion: By driving mitosis and indirectly causing microtubule disruption, the cell cycle regulatory genes *CDC25A*, *CDC25B* and *CDC2* may possess oncogenic potential. Overexpression of CDC25 occurs early in the development of oesophageal adenocarcinomas. CDC25 may serve to identify patients with malignant risk.

***Lactobacillus plantarum* sp. 299 improves gut barrier function in obstructive jaundice**

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Background: Obstructive jaundice is associated with impaired intestinal barrier function and translocation of enteric bacteria and their products to the systemic circulation. It has been suggested that probiotic bacteria, such as *Lactobacillus plantarum* sp. 299 (LP299), might improve gut barrier function by competition for attachment with indigenous microbial species and production of enterocyte trophic factors.

Methods: Baseline intestinal permeability was measured in 17 adult male Wistar rats using [^{14} C]polyethylene glycol (PEG). Animals were randomized to receive either LP299 (1×10^9 organisms; $n = 8$) or placebo ($n = 9$) daily by gavage. Standard rat chow and water were also administered under pair-fed conditions and intestinal permeability was assessed after 7 days. All animals then underwent bile duct ligation (BDL). Gavage and pair-feeding was continued for a further 7 days and intestinal permeability was measured once more. Jaundice was confirmed by measurement of serum bilirubin. Mucosal structure in both groups was assessed by morphometric analysis of sections of terminal ileum.

Results:

	Placebo	LP299
Excretion of [^{14} C]PEG before BDL (%)	0.54 (0.47–0.57)	0.51 (0.43–0.67)
Excretion of [^{14} C]PEG after BDL (%)	0.51 (0.39–0.56)	0.25 (0.22–0.30)*
Change in excretion of [^{14} C]PEG after BDL (%)	–14 (–34 to +14)	–55 (–62 to –40)*

Values are median (interquartile range). * $P < 0.01$ versus placebo (Mann-Whitney U test)

Intestinal permeability was similar in the two groups at baseline and after 7 days of feeding. Intestinal permeability was significantly reduced following BDL in animals receiving LP299 compared with those receiving placebo. There was no significant difference in mucosal morphology or mean serum bilirubin (100 versus 109 mol l^{-1}) between LP299 and placebo groups.

Conclusion: These data suggest that administration of LP299 may improve gut barrier function in the presence of obstructive jaundice.

Expression of matrix metalloproteinases 2, 3, 7, 8, 9, 12 and 14 and their tissue inhibitors (1, 2 and 3) in pancreatic adenocarcinoma

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Background: Matrix metalloproteinases (MMPs) are a group of enzymes involved in the breakdown and remodelling of extracellular matrix proteins. Their natural tissue inhibitors are known as TIMPs. Overexpression of MMPs causes excess tissue destruction and in cancer leads to tumour invasion and metastatic spread. This study aimed to investigate in detail the expression of MMPs and TIMPs in normal pancreas and in pancreatic cancer.

Methods: Formalin-fixed, paraffin-embedded blocks of normal pancreas and ductal adenocarcinoma were obtained from 55 resections. Immunohistochemistry was performed with antibodies against MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12 and MMP-14, and TIMP-1, TIMP-2 and TIMP-3 (Dako Envision method). Statistical analysis was by Fisher's exact test and Kendall's correlation.

Results: All MMPs were expressed to some degree in both normal (ten cases) and cancerous (45 cases) tissue. The expression of MMP-3, MMP-7, MMP-8 and MMP-14 was significantly increased in adenocarcinoma cells compared with normal epithelium ($P = 0.008$, $P = 0.0007$, $P = 0.047$ and $P = 0.049$ respectively). MMP-3 stromal activity was reduced in the cancer specimens ($P = 0.008$). TIMP-1, TIMP-2 and TIMP-3 were expressed in normal pancreas samples but their expression was variable in adenocarcinoma cells. TIMP-2 was expressed in 18 of 45 cancers, TIMP-3 was expressed in 43 of 45 cancers and TIMP-1 was expressed by adenocarcinoma cells in only three of 45 tumours. MMP-3 overexpression was associated with increased levels of MMP-7, MMP-8 and MMP-12 ($P = 0.003$, $P = 0.05$ and $P = 0.005$ respectively). MMP-7 was associated with overexpression of MMP-9, MMP-12 and MMP-14, and TIMP-3 ($P = 0.007$, $P = 0.042$, $P = 0.001$ and $P = 0.001$ respectively). There was also a strong correlation between MMP-14 (MT-MMP-1) and TIMP-3 ($P = 0.001$). There was no significant correlation between MMPs and TIMPs and tumour stage or grade.

Conclusion: These results suggest that the aggressive nature of pancreatic cancer may be due to the overexpression of MMPs and the downregulation of TIMPs.

Expression of cytokine-induced neutrophil chemoattractant and monocyte chemotactic protein 1 in acute pancreatitis

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Background: Inflammatory mediators play a key role in the early stages of acute pancreatitis. The role of chemokines (chemotactic cytokines) in this condition is still poorly characterized. This study investigated the temporal and spatial expression profile of the rat chemokines, monocyte chemotactic protein (MCP) 1 and cytokine-induced neutrophil che-

moattractant (CINC), in two experimental models of acute pancreatitis.

Methods: Mild acute pancreatitis was induced in adult Wistar rats by hourly intraperitoneal injection of caerulein $25 \mu\text{g kg}^{-1} \text{h}^{-1}$ over a 6-h period. Control animals received corresponding injections of saline. Severe acute pancreatitis was induced by retrograde infusion of 5 per cent sodium taurocholate into the biliopancreatic duct. Control animals received saline infusion. Localization of MCP-1 and CINC within the pancreas was determined using standard immunohistochemical techniques, while sandwich enzyme-linked immunoabsorbent assays were used to measure circulating levels of the chemokines in plasma. These experiments were conducted under a current Home Office project licence.

Results: In both the mild and severe models of acute pancreatitis, MCP-1 immunoreactivity was observed on infiltrating neutrophils and acinar cells. A subpopulation of infiltrating leucocytes was immunoreactive for CINC, while acinar cells also displayed weak labelling. MCP-1 and CINC immunoreactivity peaked 6 h following induction of acute pancreatitis. No MCP-1 or CINC immunoreactivity was observed in pancreases from control animals. Circulating plasma levels of CINC were significantly raised in caerulein-treated animals 6 h after induction (mean(s.d.) $1680(134)$ versus $725(128) \text{ pg ml}^{-1}$ in controls; $P < 0.005$, $n = 6$ in each group). In the sodium taurocholate model, circulating plasma levels of CINC were raised within 1 h of induction of acute pancreatitis ($2091(532)$ versus $1031(215) \text{ pg ml}^{-1}$ in controls; $P < 0.06$, $n = 6$ in each group).

Conclusion: These results suggest that the rat chemokines MCP-1 and CINC may mediate the local inflammatory response in acute pancreatitis. They also suggest a possible role for CINC in the subsequent systemic response.

Influence of operative environmental factors on tumour growth

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Background: The benefits of laparoscopic surgery are largely thought to result from reduced surgical trauma resulting from a smaller incision. It has been suggested that the environment of the pneumoperitoneum reduces peritoneal and surgical trauma.

Methods: To test this hypothesis, a prototype enclosed operative environment was made consisting of a perspex hood where temperature and humidity could be monitored and controlled at 37°C with humidification. This environment simulates the warm humid atmosphere encountered within the abdomen during pneumoperitoneum. Two models were used, examining both postoperative tumour growth and the inflammatory response. In the tumour model, 20 WAG rats had a 5-cm laparotomy and the abdomen was exposed to either the

open or the enclosed environment for 1 h. A suspension of 1×10^6 CC531s colon cancer cells was then injected evenly into the abdomen and the abdominal wall was closed in two layers. Control animals had tumour injection without surgery. After 3 weeks the rats were killed and an autopsy was performed to determine the extent of tumour growth. Tumour growth was assessed using the modified peritoneal cancer index and the tumour nodules were excised and weighed. In the inflammatory model, 20 WAG rats had a 5-cm laparotomy and the abdomen was exposed to either the open or the enclosed environment for 1 h. Six hours after operation the animals were killed, serum was collected and peritoneal lavage was performed. Macrophages were isolated from the lavage fluid, cultured and stimulated with endotoxin. Serum, lavage fluid and culture medium were subsequently assayed for tumour necrosis factor (TNF) α .

Results:

	Open environment	Closed environment	P*
Tumour model			
Peritoneal cancer index	13 (6–21)	9 (4–13)	0.028
Weight of excised tumour (mg)	1323 (1125–3404)	560 (32–1460)	0.04
Inflammatory model			
Serum TNF- α (pg ml^{-1})	6.3	12.7	n.s.
Peritoneal lavage TNF- α (pg ml^{-1})	43.0	45.8	n.s.
Peritoneal macrophages TNF- α (pg ml^{-1})	1278.4	2009.6	0.053

n.s., Not significant. *Mann-Whitney U test

Conclusion: Exposure of the peritoneal cavity to the ambient environment during open surgery attenuates tumour implantation. This effect may be mediated by a reduction in peritoneal trauma compared with conventional open surgery. The provision of a warmed, humidified, enclosed space may account for some of the benefits of laparoscopic surgery.

Insulin-like growth factor binding protein 3 prevents ceramide-induced apoptosis in human breast cancer cells

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Background: Cytotoxic drugs used in cancer therapy induce apoptosis in tumours and this action correlates with the efficacy of the agents. Ceramide acts as a second messenger in the apoptotic signalling pathway for some of these drugs. This action can be mimicked using a synthetic ceramide analogue (C2). Transforming growth factor (TGF- β) inhibits cell growth through induction of insulin-like growth factor binding protein (IGFBP) 3, which is the main carrier protein for the insulin-like growth factors. It was previously demonstrated that exogenous IGFBP-3 can accentuate C2-induced cell

death. This study aimed to investigate the interaction of C2 with TGF- β -induced endogenous IGFBP-3 in human breast cancer cells.

Methods: (1) Hs578T human breast cancer cells were treated with TGF 5 ng ml⁻¹ for 5 days with and without C2 20 mol l⁻¹ for the final 24 h. Growth inhibition was assessed by trypan blue counts and endogenous IGFBP-3 was measured by radioimmunoassay of the conditioned media. Apoptosis was measured by trypan blue counts and flow cytometry. (2) Dosing was repeated as above with 20 g ml⁻¹ antisense messenger RNA (mRNA) to IGFBP-3 added on days 1, 3 and 5 with the same assessments.

Results: (1) TGF- β alone caused no cell death but a 53 per cent inhibition of cell growth ($P < 0.01$) and a significant increase in endogenous IGFBP-3 from 77 to 906 ng ml⁻¹ in control cells ($P < 0.001$). The number of cells in the pre-G1 phase decreased dramatically from 63 per cent when treated with C2 alone, to 14 per cent in cells incubated with TGF- β and C2 ($P < 0.001$). (2) Antisense mRNA caused a reversal of this antiapoptotic effect, with a significant increase in cells in pre-G1 ($P < 0.001$). The antisense mRNA caused a significant decrease in endogenous IGFBP-3 to 370 ng ml⁻¹ ($P < 0.001$).

Conclusion: Although exogenous IGFBP-3 accentuates C2-induced apoptosis, the same was not true for endogenously produced IGFBP-3. The increased amount of IGFBP-3 totally blocked C2-induced apoptosis. These findings may have important implications for optimizing the efficacy of cancer therapy particularly with regard to combination chemotherapy.

Pretreatment identification of patients most likely to benefit from induction chemotherapy

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Background: Induction chemotherapy is being used with increasing frequency in patients with breast cancer. Clinical responses are high although pathological responses (predictors of survival) are much lower. There is a need to establish predictors of likely response before commencement of chemotherapy. This study aimed to define biological criteria for predicting the response to induction chemotherapy in patients with breast cancer.

Methods: Histopathological variables were studied on core biopsies taken from 106 patients with breast cancer before induction chemotherapy. Tumours were typed and graded. Immunohistochemistry was carried out using a standard three-stage avidin biotin peroxidase complex technique to detect hormone receptors (oestrogen, ER; progesterone), a proliferation marker (MIB-1), an oncoprotein (c-erb2), an extracellular matrix degradation enzyme (cathepsin D) and an oestrogen-associated protein (pS2). Operative specimens were assessed for pathological response.

Results: Univariate analysis revealed that c-erb2 positivity ($P = 0.0009$) and ER negativity ($P = 0.003$) identified patients who had a complete response. Multivariate analysis revealed that c-erb2 positivity ($P = 0.01$) and ER negativity ($P = 0.009$) independently predicted a good pathological response.

Conclusion: These markers may be clinically useful in predicting the likelihood of a beneficial response to induction chemotherapy and patients most likely to benefit from induction chemotherapy may be identified.

Significantly enhanced response with docetaxel as primary chemotherapy in patients with breast cancer

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Background: Primary chemotherapy is commonly used to treat breast cancer. The most efficacious drug regimens utilize anthracyclines, but many cancers fail to respond. This study aimed to determine the efficacy of primary docetaxel treatment in patients with breast cancer.

Methods: Patients with breast cancer received four pulses of cyclophosphamide, doxorubicin, vincristine and prednisolone (CVAP) chemotherapy. Clinical response was then assessed. Those with a partial (PR) or complete (CR) clinical response were randomized to receive either four further pulses of CVAP or four pulses of docetaxel. All patients whose tumours failed to respond received four further pulses of docetaxel. Following this chemotherapy regimen, clinical response was assessed and surgery was carried out. Pathological response was assessed in the resected breast tissue.

Results: One hundred and seventy patients have been enrolled into the study, of whom 105 were suitable for randomization. In randomized patients after completion of chemotherapy, the clinical PR or CR rate was 67 per cent in the CVAP group and 96 per cent in the docetaxel group ($\chi^2 = 12.57$, $P < 0.001$). Non-randomized patients had a clinical PR or CR of 43 per cent. Pathological response in randomized patients was 43 per cent with CVAP and 78 per cent with CVAP and docetaxel ($\chi^2 = 2.05$, $P = 0.15$); in non-randomized responders it was 42 per cent.

Conclusion: Primary treatment with docetaxel resulted in substantial and significantly increased clinical and pathological responses. Of patients who failed to respond to CVAP, 42 per cent responded to subsequent docetaxel therapy.

Oestrogen receptor B as a new form of oestrogen receptor in breast cancer

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Background: The female hormone, oestrogen, mediates its multiple effects via binding to the nuclear transcriptional factor

oestrogen receptor (ER). For many years the ER status of breast cancer has been used both as a predictor of response to hormone therapy and as a prognostic indicator. A new form of ER, known as ER- β , has been described recently. The aims of this study were to investigate the distribution and possible clinical significance of this new form of ER in breast cancer.

Methods: The classical ER (now known as ER- α) and ER- β were measured using reverse transcriptase-polymerase chain reaction.

Results: ER- β expression was found in 26 (51 per cent) and ER- α was present in 37 (73 per cent) of 51 primary breast cancers. No correlation was found between either the presence or level of ER- α or ER- β , suggesting independent expression of the two receptor forms. ER- α ($r=0.45$, $P=0.002$, $n=48$), but not ER- β , levels correlated significantly with levels of ER protein determined by enzyme-linked immunosorbent assay (ELISA). In addition, ER- α but not ER- β was found more frequently in carcinomas positive for ER protein than in those negative for the protein ($\chi^2=12.2$, $P=0.0005$).

Conclusion: ER- β is expressed in approximately 50 per cent of primary breast carcinomas and this expression appears to be independent of ER- α . The ELISA routinely used for detecting ER appears to primarily measure the ER- α form.

Proliferation in normal breast epithelium is decreased by epidermal growth factor receptor inhibition

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Background: The factors controlling epithelial proliferation in the normal breast remain unknown. This study aimed to determine if blocking epidermal growth factor receptor (EGFR) with an EGFR tyrosine kinase inhibitor (ZD1839) affects epithelial proliferation in normal breast tissue.

Methods: Normal tissue taken from 15 women (all EGFR positive) undergoing surgery was implanted into 16–20 athymic nude mice per experiment (eight xenografts per mouse) and daily gavage with either ZD1839 at 50–200 mg kg⁻¹ or vehicle for 14 days was commenced 2 weeks after implantation. Xenografts were removed on days 14, 21 and 28. Pellets of 17-oestradiol (2 mg) were implanted subcutaneously in a second set of experiments on day 14 in

both control and treatment mice. Epithelial proliferation was assessed by counting 1000 cells after immunostaining with Ki67.

Results: ZD1839 inhibited proliferation at all doses compared with controls after 14 days ($P<0.05$). Proliferation was similarly inhibited in normal epithelia stimulated with oestradiol when treated with ZD1839 (75–100 mg kg⁻¹) compared with controls ($P<0.001$).

Conclusion: EGFR inhibition blocks not only oestrogen-stimulated but also constitutive epithelial proliferation of the breast. EGFR tyrosine kinase inhibitors have potential as chemopreventative agents.

E1AF transcription factor level is increased in breast cancer

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Background: The transcription factor E1AF (also known as PEA3) is a member of the Ets family of transcriptional factors. These transcriptional factors may be important in cancer progression as they control the expression of key genes involved in metastases, i.e. proteases and adhesion proteins. It was hypothesized that E1AF might show increased expression in malignant breast tissue compared with non-malignant breast tissue and that this increased expression would correlate with pathological parameters of breast cancer progression. The aim of this study was to measure E1AF messenger RNA (mRNA) levels in human primary breast carcinomas and to compare these levels with those found in fibroadenomas and in normal breast tissue.

Methods: Using semiquantitative reverse transcriptase-polymerase chain reaction, E1AF mRNA levels were measured in 120 invasive breast carcinomas, 20 fibroadenomas and 11 normal samples of breast tissue.

Results: Expression of E1AF was not found in any of the 11 normal specimens of breast tissue but was detected in six of 20 fibroadenomas and 50 of 120 carcinomas. The *E1AF* gene was expressed more frequently in breast carcinomas than in non-malignant breast tissue ($\chi^2=4.02$, $P=0.04$). E1AF expression was significantly higher in malignant tissue (0.14 (range 0–2.82) units) than non-malignant breast tissue (0.03 (range 0–

	Ki67 labelling index (%)					
	Day 0	Day 14	Day 21		Day 28	
			Control	ZD1839	Control	ZD1839
With oestrogen	0.4 (9.8–10.4)	7.2 (5.1–8.3)	15.7 (10.7–18.3)	1.5 (0.5–4.3)†	—	—
Without oestrogen	7.6 (4.4–12.9)	3.9 (3.1–6.1)	3.3 (0.8–4.8)	0.7 (0–1.3)*	6.1 (3.4–7.8)	1.8 (0.7–3.9)*

Values are median (interquartile range). * $P<0.05$, † $P<0.001$ (analysis of variance)

0.46) units) ($P=0.02$, Mann-Whitney test). E1AF did not correlate with tumour size, grade or oestrogen or progesterone receptor status. There was an inverse correlation between E1AF mRNA expression and nodal involvement ($r_s=-0.26$, $P<0.01$).

Conclusion: The inverse relationship between E1AF mRNA levels and nodal metastases is surprising and not consistent with data from model systems. There is higher expression of the *E1AF* gene in breast carcinomas than in non-malignant breast tissue.

New surveillance molecules in breast cancer

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Background: There is an urgent need to identify single genes or patterns of overexpressed genes common to the majority of breast tumours both as prognostic markers and as therapeutic targets.

Methods: Differential display polymerase chain reaction (PCR) was used to compare the gene expression patterns in primary normal breast luminal epithelial cells and in breast tumour cells that had been immunomagnetically sorted *in vitro* to produce cell populations greater than 90 per cent pure. RNA was prepared from four to five samples of both normal luminal epithelial cells and purified breast tumour cells. Differential display PCR was performed under standard conditions and 30 bands were identified which were upregulated in at least three-quarters of the tumour cell preparations. Each of these bands was excised, reamplified and cloned. One-third of the bands represented known messenger RNAs (mRNAs), while two-thirds were unknown messages with expressed sequence tag homologies. Differential expression was confirmed by conventional semiquantitative reverse transcriptase (RT)-PCR using primers designed from within the differentially displayed sequence. Genes confirmed to be differentially expressed in these RNA preparations were screened by RT-PCR for their pattern of expression in normal breast tissue from reduction mammoplasty ($n=20$), in solid breast tumours ($n=40$), in a panel of normal human tissues and in 28 breast cancer cell lines. In the latter case, expression was compared with that of known tumour markers.

Results: One of the first bands identified corresponded to cyclo-oxygenase 2 (*cox-2*), which has recently been shown to be upregulated in several gastrointestinal cancers and also in breast cancer. Other genes upregulated in breast tumour cells

included a regulator of G-protein signalling, *BL34*, and a novel DNA damage checkpoint kinase, *cds-1*. These genes represent surveillance molecules which are upregulated in breast tumours in response to increases in inflammation, local growth factor signalling and DNA damage.

Conclusion: Rapid amplification of cohesive ends PCR was used to quickly clone potentially full-length complementary DNAs representing novel differentially expressed mRNAs and express them in different cell backgrounds using the T-REX tetracycline-inducible expression system (InVitrogen). This approach will allow the functional characterization of these new molecules and determine what role they play in the aetiology and progression of breast cancer.

Imprint cytology and the sentinel node in breast carcinoma

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Background: Sentinel lymph node (SLN) biopsy is gaining increasing acceptance in the management of patients with breast carcinoma. Absence of a rapid and reliable intraoperative diagnostic tool to determine the status of the SLN is a major limiting factor.

Methods: After excision of the SLN, it was halved and the cut surface touched on to a clean slide. The slides were stained with rapid cytological stain (RAL 555; Cell Path, UK). Some of the materials from imprints were left for special stains and immunocytochemistry.

Results: A total of 59 sentinel nodes were biopsied in 47 patients (mean 1.3 per patient). Nine patients (19 per cent) were found to have nodal metastasis on definitive histological examination of the SLN. Imprint cytology correctly predicted the nodal status in 45 of 47 cases. In one patient there was evidence of micrometastasis detected by immunohistochemistry, which imprint cytology failed to detect. In another patient rapid staining showed some suspicious cells but immunocytochemical staining was negative. There were no false-positive cases.

Conclusion: This initial experience with imprint cytology is encouraging and the technique may be used as an adjunct or substitute to frozen-section histology. Intraoperative immunocytochemistry may be used to improve the diagnostic accuracy of this method. Significant experience is required and both the surgeon and the pathologist should be aware of the potential pitfalls in diagnosis.

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double spacing

Prognosis after breast recurrence following conservative surgery and radiotherapy in patients with node-negative breast cancer

Sir

I read with interest the article by Francis *et al.* (*Br J Surg* 1999; 86: 1556–62). It is always disconcerting to meet a patient with breast recurrence following conservative surgery for cancer. The authors begin by saying 'large randomized trials have shown equivalent survival, stage for stage, for patients with breast cancer treated with conservative surgery and radiation therapy compared with total mastectomy and axillary dissection'. While this statement is true, it does not mean that the clinical outcome is the same in both groups.

In 1996 I was impressed by a letter in the *British Medical Journal* warning against a wholesale switch to conservative surgery for breast cancer¹. Two articles (also in the *BMJ*) written by patients highlighted the fact that for many women, loss of the breast may not be as great a concern as the fear of recurrence, chemotherapy, radiation, etc^{2,3}. In the present climate of minimal surgery and specialist breast units, surgeons often regard total mastectomy, and therefore the inability to conserve the breast, as a failure. I suspect that this is often the perception of the doctor, not the patient. Many patients have been persuaded to conserve their breasts when they may not have objected to total removal.

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1 Benson EA. Reservations about conservative surgery for early breast cancer. *BMJ* 1996; 312, 845–6.

2 Friederberger J. The false breast: should we go for it so quickly? *BMJ* 1996; 313: 1014–15.

3 Reed J. I lost my breast but is anyone to blame? *BMJ* 1998; 316: 400–1.

Authors' reply

Sir

We agree with Mr van Langenberg's comment that, for many women, the loss of a breast through mastectomy may not be as great a concern as the fear of recurrence. The series that we presented includes closely-followed patients seen between November 1979 and December 1994, with a median follow-up of 6 years. The study provides important outcome data about prognosis after a recurrence in the breast and, thus, equips clinicians to advise women about the risks and benefits of breast conservation.

We do not offer breast conservation to all patients – to do so would be inappropriate – and we would be as concerned by surgeons whose breast conservation rates were close to 100 per cent as we would by those whose mastectomy rates were close to 100 per cent. How much informed choice is being made in these situations? In a previous report we showed (a cohort of women treated in 1992, of whom 55.7 per cent were treated with breast conservation for tumours of less than 2 cm and 44.3 per cent with a total mastectomy) that the main predictor for mastectomy was the surgeon's case load. Mastectomy rates ranged from 60 to 80 per cent if the surgeon treated fewer than eight patients with breast cancer per year and about 45 per cent if more than eight patients were treated¹.

At the Westmead Breast Centre, all women are reviewed before operation in a multidisciplinary team setting. The women are seen by an experienced breast surgeon and either a breast radiation oncologist and/or medical oncologist. An individualized care plan is developed after review at a multidisciplinary case conference and the women are supported by counselling and nursing staff. When a choice between mastectomy and breast conservation is an option women are given objective verbal, written and, often, web-based explanations of the risks and benefits of each treatment (New South Wales Breast Cancer Institute's Internet site, BreastNet, is located at <http://www.bci.org.au>).

It is essential that women be given time to understand their options and the opportunity to make informed decisions that will help them to develop a more positive outlook to their disease.

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1 Taylor R, Stubbs J, Langlands AO, Boyages J. Predictors of mastectomy for women with breast cancer in the Greater Western Region of Sydney. *Breast J* 1999; 5: 116–21.

Endoscopic technique for the localization of intraduct papillomas

Sir

We were interested in the technique suggested by Domínguez-Cunchillos *et al.* (*Br J Surg* 1999; 86: 1470–1) but were surprised to learn that ductograms are still used in the investigation of patients with suspected papillomas. We recently carried out a 2-year audit of the reliability of ductograms in predicting pathology associated with single duct nipple discharge and found that they accurately predicted pathology in only 38 per cent of patients. We have abandoned their use in our department. We would be interested to know whether the two procedures in which a papilloma was not

identified endoscopically or pathologically were performed on the basis of evidence from ductograms alone.

The authors state that the endoscopic placement of a guidewire perioperatively guaranteed removal of the duct papilloma. The discharging duct still had to be identified by conventional means, however, in order to pass the guidewire, dilate the duct and insert the endoscope. They did not, or were unable to, examine the other surrounding ducts when endoscopy of the discharging duct was negative and a macrodoectomy was performed on purely ectatic ducts. No papillomas were identified in these patients.

We recommend nipple discharge cytology as the investigation of choice in the investigation of single duct nipple discharge as it is helpful in 67 per cent of patients¹. Most intraduct papillomas are located near the nipple/areola complex and their operative visualization before microdoectomy seems unnecessary.

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- 1 Fung A, Rayter Z, Fisher C, King DM, Trott P. Preoperative cytology and mammography in patients with single-duct nipple discharge treated by surgery. *Br J Surg* 1990; 77: 1211–12.

Author's reply

Sir

We thank Drs Vestey and Rayter for their interest in our technique but, as stated in our short note, ductoscopy was used to confirm the diagnosis and identity of the duct to be removed. Endoscopy of the lactiferous duct only confirms the diagnosis, previously made by evaluation of symptoms, ductogram and discharge cytology. Eliciting the discharge by expression of the breast is sufficient to identify the appropriate duct to initiate endoscopy.

Endoscopy at least allows deeper examination within the breast and may identify correctly the smaller branches containing a papilloma.

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Endoscopically assisted, minimally invasive parathyroidectomy

Sir

We read with interest the article by Gauger *et al.* (*Br J Surg* 1999; 86: 1563–6). Some caution is necessary when dealing with emerging surgical techniques but the scepticism seemed a little exaggerated. On the basis of our experience with over 130 patients we wish to discuss the conclusions of the paper.

First, the higher rate of complications in patients undergoing endoscopic procedures only is apparent. The absence of wound infection, haematoma and transient hypoparathyroidism must be regarded as relevant advantages peculiar to the minimally invasive technique as previously documented¹. The transient laryngeal nerve palsy can be attributed to the small experience with a new procedure. This complication remains a sporadic report.

Second, we agree that further studies are required examining the two advantages expected from this operation: a better cosmetic result and less postoperative pain. The classical bilateral open procedure has been compared with minimally invasive video-assisted parathyroidectomy (MIVAP) for patient's satisfaction for cosmesis and postoperative distress. MIVAP proved to have a statistically significant better outcome².

Third, the possibility of missing multiglandular disease should be evaluated under two conditions: (1) by using the quick intraoperative parathyroid hormone assay, and (2) in the absence of preoperative imaging the surgeon should be able to explore the opposite side without converting to the open procedure. Rather than using the technique of Gauger *et al.* we advocate a central access which allows easy bilateral exploration³.

Finally, the observation that all recent experiences with minimally invasive surgery in the neck would be market-driven seems groundless in countries where a national health system operates.

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- 1 Lorenz K, Nguyen-Thanh P, Dralle H. First experience with minimally invasive video-assisted parathyroidectomy. *Acta Chir Austriaca* 1999; 30: 218–20.
- 2 Miccoli P, Bendinelli C, Bertu P, Vignali E, Pinchera A, Marcocci C. Video-assisted *versus* conventional parathyroidectomy in primary hyperparathyroidism: a prospective randomized study. *Surgery* 1999; 126: 1117–22.
- 3 Miccoli P, Bendinelli C, Conte M, Pinchera A, Marcocci C. Endoscopic parathyroidectomy by a gasless approach. *J Laparoendosc Adv Surg Tech A* 1998; 8: 189–94.

Authors' reply

Sir

We certainly agree with the sentiment expressed by Dr Miccoli and colleagues that 'caution is necessary when dealing with emerging surgical techniques', and it is for that reason that we have maintained a degree of scepticism about endoscopically assisted minimally invasive parathyroidectomy. Indeed, we are currently part way through a prospective randomized trial of

the 'focused' approach to minimally invasive parathyroid surgery (a 2.5-cm scan-directed lateral incision directly over the adenoma) compared with the endoscopically assisted approach. Our early experience of the simple scan-directed approach has reinforced our view that the use of endoscopic techniques in the neck may be more of a surgical 'gimmick' than a useful therapeutic alternative. When considering the influence of market forces it should be acknowledged that the 'market' includes patients themselves wishing to have access to new technology, as well as surgeons wishing to increase referrals to their academic centres and numbers of patients in their series – 'market forces' are not just confined to private practice-based medical systems.

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Epidemiology of Warthin's tumour of the parotid gland in an Asian population

Sir

The article by Chung *et al.* (*Br J Surg* 1999; 86: 661–4) and the letter from Renehan *et al.* (*Br J Surg* 1999; 86: 1480) emphasize that the aetiology of adenolymphoma (Warthin's tumour) remains uncertain. The possible relevance of smoking^{1,2} has received further support from the study by Chung *et al.* Their incidence of adenolymphoma in a population of heavy smokers from Singapore is higher (25 per cent of parotid tumours) and with a greater tendency to bilaterality (9.5 per cent) than that seen in Bristol. Of 93 neoplasms in 89 patients studied between 1951 and 1995, bilaterality ranged from 3 to 5 per cent over time, with a pleomorphic: adenolymphoma ratio of 3:1 (Singapore figure 1.9:1).

We are perplexed by the suggestion that Epstein-Barr virus (EBV) might be implicated and understand that, in common with South-East Asia, EBV infection is endemic within the UK population from exposure during childhood and adolescence. Of the 89 patients in Bristol there were only two young women aged 19 and 20 years (both heavy smokers) and three in the fourth decade. Otherwise the mean age at presentation was 59 years in women and 58 years in men. It is unlikely, therefore, that active EBV infection could be an aetiological factor. Are the findings of Renehan *et al.* merely evidence of past infection? The 'smoking hypothesis' offers a more logical explanation for the well documented change in male/female incidence over the past 50 years¹. In both our study groups^{1,3} light smokers (5–10 cigarettes per day) and ex-smokers were also at risk, with some of the latter producing adenolymphomas over 10 years later. The aetiology of these interesting tumours deserves further study.

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- 1 Ebbs SR, Webb AJ. Adenolymphoma of the parotid. aetiology, diagnosis and treatment. *Br J Surg* 1986; 73: 627–30.
- 2 Cadier M, Watkin G, Hobsley M. Smoking predisposes to parotid adenolymphoma. *Br J Surg* 1992; 79: 928–30.
- 3 Lewis DR, Webb AJ, Lott MF, Brookes ST, Farndon JR. Improving cytological diagnosis and surgical management of parotid adenolymphoma. *Br J Surg* 1999; 86: 1275–80.

Prospective study of chronic pain after groin hernia repair

Sir

Callesen *et al.* (*Br J Surg* 1999; 86: 1528–31) are to be congratulated on calling our attention to the vexing problem of chronic and persistent pain after groin hernia repair. Of their 419 patients, 19 per cent had some pain and 6 per cent had moderate or severe pain 1 year after operation. In the study by Cunningham *et al.*¹, 62.9 per cent had some groin or inguinal pain and 11.9 per cent had moderate to severe pain at 1 year, while 53.6 per cent had pain and 10.6 per cent reported moderate to severe pain 2 years after operation.

Considering that the incidence of preoperative pain might not have been very different from the frequency of chronic postoperative pain, it is sad and disappointing that a better outcome is not forthcoming. It has been my experience that unyielding polypropylene or nylon sutures are an important cause of persistent postoperative pain of the type described in the studies cited above. Removal of such sutures often, if not invariably, provides instantaneous relief. It is unfortunate that the important detail of the type of suture has been overlooked and not addressed, even though the association of pain with unyielding sutures has been noted in other types of incisions². Future studies should scrutinize the precise manner of suturing used in the repair.

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- 1 Cunningham J, Temple WJ, Mitchell P, Nixon JA, Preshaw RM, Hagen NA. Cooperative hernia study. Pain in the postoperative patient. *Ann Surg* 1996; 224: 598–602.
- 2 Cameron AEP, Parker CJ, Field ES, Gray RCF, Wyatt AP. A randomized comparison of polydioxanone (PDS) and polypropylene (Prolene) for abdominal wound closure. *Ann R Coll Surg Engl* 1987; 69: 113–15

Peripheral Endovascular Interventions. 2nd ed.

R. A. White and T. J. Fogarty (eds)

259 × 182 mm Pp 640 Illustrated 1999 New York Springer £114 50

This is the second edition of a text first published by Mosby in 1996. It is almost exclusively American in nature and style, with only 12 of the 60 authors coming from outwith the USA. Despite its unambiguous title it was difficult to identify its target readership. Chapters on lower-limb angioplasty have largely been written by surgeons (which accounts for their conservative attitude); there is quite a contribution from cardiologists and a disproportionate amount on atherectomy devices (12 pages), intravascular ultrasound (21 pages) and even balloon embolectomy (19 pages).

This is not a 'practical text'. I had expected to review chapters on the management of difficult clinical problems, such as early and late endoleaks, but 269 pages elapsed before the first clinical chapter was encountered. Endoleak management was not reviewed in any detail at all, nor were there any references to the large European registries of complications after endovascular aneurysm repair. There are, however, some extremely good contributions, including chapters on the problem of training in endovascular surgery (25 per cent of surgical programme directors said their interventionists would not train vascular surgery trainees), the endovascular repair of thoracic aneurysms and the prevention of recurrent stenoses within endovascular devices. On the negative side, there was almost a total lack of evidence within the chapters, particularly regarding the role of stents. For example, several authors still referred to Richter's randomized trial as justification of the benefits of iliac stenting, despite the fact that it appeared only in abstract form 9 years ago and has never been published as a main article. Moreover, in chapter 39, we are told that stents reduce acute complications and late restenosis. However, within the same paragraph (and using the same references) we are also informed that multiple studies have demonstrated that stenting increases late lumen loss (which I presume means restenosis). Similarly, although we are advised that angioplasty of the infrapopliteal segment should only be undertaken as a limb salvage procedure in high-risk patients, it is still possible to report an 84 per cent improvement in critical limb symptoms at 6 years. Finally, the most intriguing aspect of this book comes in the section on carotid angioplasty. While discussing the results of Theron (who developed a distal protective balloon system to prevent embolization), Dietrich appears to suggest that, while no embolic complications have been reported by Theron, he has 'personal knowledge' of complications that have occurred.

In summary, this book is an overview of all that is possible via the endovascular route, but not of the corroborative evidence (much of which is, understandably, not yet available). While on occasions it seems to lack clinical reality (such as the role of angiography to identify the saphenofemoral junction in recurrent varicose veins), one must applaud the author who managed to

refer to the 'Perclose' device 57 times in his 12-page chapter on the management of the percutaneous access site.

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Minimal Access Cardiothoracic Surgery

A. P. C. Yim, S. R. Hazelrigg, M. B. Izzat, R. J. Landreneau, M. J. Mack, K. S. Naunheim (eds).

286 × 220 mm Pp 693 Illustrated 2000 Philadelphia, Pennsylvania. WB Saunders £110

Minimal access approaches have been the areas of greatest growth and innovation in cardiothoracic surgery in recent years, testing surgical and technical ingenuity to their limits. Many surgeons have been sceptical about the wisdom of certain minimal access approaches in cardiac surgery, which expose the patient to additional risks in order to shave only a few centimetres off the length of a skin incision. There is also concern about the lack of randomized trials comparing minimal access to traditional approaches. Nevertheless, there is great interest in these new approaches and this book is therefore timely. It is written by enthusiasts, each of whom has made major contributions in his own field. The enthusiasm of the authors is balanced to some extent by an objective commentary (sometimes more than one) at the end of many chapters, which helps to place the subject matter in context. Some of these commentaries are excellent and they represent one of the best features of this book.

The volume is predominantly technical, covering the whole range of pulmonary, mediastinal, oesophageal and cardiac procedures that can be performed through minimal access. Robotic surgery has its own chapter, and there are also chapters on anaesthesia, interventional radiology and myocardial function during beating heart surgery. In all, there are 83 chapters and 174 contributing authors (possibly a record), some of whom have provided only commentaries. With so many authors it is inevitable that the standard of chapters varies, but most are well written. In general, the black and white illustrations are clear but some of the colour operative photographs are of poor quality. The six editors are to be congratulated for assembling such a uniquely comprehensive volume that encapsulates the present state of knowledge. Every surgeon with an interest in minimal access approach will learn much from the experts and pioneers in this field. However, the foreword to the book emphasizes that this is a rapidly changing field and even looks forward to the second and subsequent editions. For this reason, this text is perhaps more suitable for a library than for individual purchase.

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Plastic and Reconstructive Breast Surgery. 2nd ed. (Two volumes)

J. Bostwick III

285 × 223 mm Pp. 1606 Illustrated 2000 St Louis, Missouri. Quality Medical Publishing Price not supplied

Although labelled the second edition, this is in fact the third version of John Bostwick's excellent book. This is a single author tome consisting of two separate books that can be divided essentially into reconstructive and aesthetic surgery. Dr Bostwick has likened the development of this work to running a marathon (something he excels in) and one can tell that this is both a labour of love and an authoritative volume. The introductory section (especially that dealing with difficult patients and medicolegal matters) should be essential reading for any surgeon, let alone those interested in this aspect of breast surgery. Why should someone buy the second edition if they have access to the first? All sections have been improved. There are better illustrations and newer techniques are discussed, including that of endoscopic breast surgery which was pioneered in Atlanta. One or two minor disappointments remain. There is relatively little on partial breast reconstruction and there is some repetition and overlap. These books are expensive but their worth is unquestionable.

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Crucial Controversies in Surgery. Volume 3

M. Schein and L. Wise (eds)

234 × 153 mm Pp 299 Illustrated. 1999 Philadelphia, Pennsylvania. Lippincott, Williams and Wilkins \$49.95.

In volume 3 of this series the specific aim of the authors is to address ever-evolving dilemmas in surgery. The editors have selected a wide range of specialty interests: general, vascular, bowel and endocrine surgery. There are useful and germane discussions that highlight the difficulties surrounding generalized issues such as surgical technical education, evidence-based surgery, and infection in the intensive care unit. Each subject is addressed as a pithy discourse by between one and three sets of authors in a current area of major controversy, such as complex diverticular disease, obstructive jaundice and the management of parathyroid disease. Following this there is an invited commentary to balance and structure the arguments. Finally, there is an editorial comment to round up each subject.

The book is well referenced and there is a good deal of evidence-based medicine, in addition to surgical direction based on interesting personal experience. This work should be of great interest to the specialist surgeon and to candidates sitting examinations such as the Intercollegiate Speciality

Examination in the UK. However, this book requires a good basic understanding of the management of the subjects discussed as, inevitably, it is written in a highly concentrated fashion.

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Jones' Clinical Paediatric Surgery. Diagnosis and Management. 5th ed.

J. M. Hutson, A. A. Woodward, S. W. Beasley (eds)

243 × 189 mm. Pp. 331. Illustrated. 1999. Carlton South, Australia: Blackwell Science Asia. £35.

Undergraduate textbooks of surgery generally accommodate children's conditions as a prefix or suffix to the adult chapter. There is, therefore, a market for a text which aggregates paediatric surgical conditions and provides some information on prevalence and complexity. This book claims to be directed at undergraduates and junior hospital doctors; it has achieved incorporation of the important surgical conditions of children in a readable format, with the added intellectual challenge of a multiple choice question case scenario as an introduction to each chapter. However, repetition between chapters (fluid management/acid base derangement/posterior urethral valves/temperature control) diminishes its impact and there are surprising omissions, such as informed consent and the issue of ethics in children's care. While a text of this size cannot be comprehensive, perhaps some of the 100 or more pages dealing with surgical neonatology could be assigned to these issues. It is difficult to distinguish the common from the rare in this work, for instance, sexual ambiguity receives almost as much coverage as inguinal hernia. However, apart from the undue emphasis on neonatal specialist care, it does achieve lucid description of contemporary management in most surgical specialties dealing with children; the section on paediatric orthopaedics is particularly good. There is a void in the undergraduate market which this text partially fills. The emphasis on specialist conditions detracts from it being a resource for those requiring broad-based essential knowledge, such as students and general practitioners, and places it more appropriately in the domain of those involved in preparatory training for surgery in general, and paediatric surgery in particular.

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Scientific Surgery

Mandel J, Church T, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. *J Natl Cancer Inst* 1999; **91**: 434–7.

Late follow-up of the Minnesota screening trial involving over 46 000 patients showed that annual screening reduced the 18-year colorectal cancer mortality rate by 33 per cent and biennial screening by 21 per cent, compared with controls.

Robinson MHE, Hardcastle JD, Moss SM, Amar SS, Chamberlain JO, Armitage NCM *et al.* The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer. *Gut* 1999; **45**: 588–92. This study evaluated the harm done by a screening programme including 75 000 people. Seven patients had a major complication after colonoscopy, six needed surgery, none died. No patient without colorectal cancer died

Toouli J, Roberts-Thomson IC, Kellow J, Dowsett J, Saccone GTP, Evans P *et al.* Manometry based randomised trial of endoscopic sphincterotomy for sphincter of Oddi dysfunction. *Gut* 1999; **45**: 98–102.

Some 26 of 81 patients with biliary-type pain after cholecystectomy had sphincter stenosis identified by manometry. Sphincterotomy improved symptoms in 11 of 13 compared with five of 13 controls ($P=0.41$)

Gibbs PJ, Foy DMA, Darke SG. Reoperation for recurrent saphenofemoral incompetence: a prospective randomised trial using a reflected flap of pectineus fascia. *Eur J Vasc Endovasc Surg* 1999; **18**: 494–8.

Forty legs (37 patients) were randomized. Duplex imaging a minimum of 18 months later revealed that the pectineus flap failed to reduce the rate of groin recurrence

Nagelschmidt M, Fu ZX, Saad S, Dimmeler S, Neugebauer E. Preoperative high dose methylprednisolone improves patients' outcome after abdominal surgery. *Eur J Surg* 1999; **165**: 971–7.

Twenty patients having abdominal surgery were included. A single dose of methylprednisolone (30 mg/kg) given 1 h before operation significantly improved outcome and reduced hospital stay by an average of 4.5 days.

Meng WCS, Leung KL, Ho RLK, Leung TWT, Lau WY.

Prospective randomized controlled study on the effect of branched-chain amino acids in patients with liver resection for hepatocellular carcinoma. *Aust N Z J Surg* 1999; **69**: 811–15.

Fifty patients were enrolled into this trial of additional postoperative nutrition. The study group had a shorter hospital stay and significantly improved nutritional indices, but there was no difference in morbidity or mortality.

Laterza E, de' Manzoni G, Veraldi GF, Guglielmi A, Tedesco P, Cordiano C. Manual compared with mechanical cervical oesophagogastric anastomosis – a randomised trial. *Eur J Surg* 1999; **165**: 1051–4.

Some 41 operations were studied – three of 20 stapled anastomoses leaked compared with one of 21 that were hand-sewn. The stricture rate was three and two respectively

Heymen S, Wexner SD, Vickers D, Nogueras JJ, Weiss EG, Pikarsky AJ. Prospective randomized trial comparing four biofeedback techniques for patients with constipation. *Dis Colon Rectum* 1999; **42**: 1388–93.

There were no significant differences between the four different methods of biofeedback investigated in this trial including 36 patients. All were equally effective

Neilson RL. Meta-analysis of operative techniques for fissure-in-ano. *Dis Colon Rectum* 1999; **42**: 1424–7.

Seventeen publications of comparisons between at least two techniques, including 2727 patients were analysed. Internal sphincterotomy was superior to anal stretch, both in terms of rates of recurrence and incontinence

Shimada K, Ajani JA. Adjuvant therapy for gastric carcinoma patients in the past 15 years: a review of western and oriental trials. *Cancer* 1999; **86**: 1657–68.

All randomized controlled trials since 1984 were reviewed. Despite 30 years of study the authors state that postoperative chemotherapy remains investigational

Senkal M, Zumtobel V, Bauer K-H, Marpe B, Wolfram G, Frei A. Outcome and cost effectiveness of perioperative immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. *Arch Surg* 1999; **134**: 1309–16.

The trial included 154 patients. Perioperative immunonutrition significantly reduced the rate of infective complications (14 *versus* 27, $P=0.05$) and lowered the costs of treatment.

Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LLM, Blankensteijn JD *et al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *N Engl J Med* 1999; **341**: 1789–94.

Some 112 patients at high cardiac risk were included. Mortality (3.4 *versus* 17 per cent, $P=0.02$) and non-fatal myocardial infarction (0 *versus* 17 per cent, $P<0.001$) were reduced by beta-blockade.

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The Editors welcome topical correspondence. Letters should not exceed 250 words and should be typed double-spaced.

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This must not exceed 200 words and should be presented in a structured format. **Background:** state why the study was done and its main aim. **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study, i.e. randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings including important numerical values. **Conclusion:** state the main conclusions but controversial or unexpected observations may be highlighted.

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For detailed guidance on the handling of statistical material consult *Br J Surg* 1991; 78: 782-4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, the chosen end-points and justify the sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; 276: 637-9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished and presented in parentheses after the mean values.

Analysis

Clearly describe methods used for each analysis. Methods not in common usage should be referenced. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value. Actual *P* values should be reported to two decimal places, especially when the result is not significant. The results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Take great care in your interpretations. Do not place undue emphasis on secondary analyses.

References

Type the references with double spacing in the Vancouver style (see **Preparation of manuscripts**). Reference to abstracts and personal communications is discouraged. Reference to unpublished communications will not be accepted.

In the text, number references consecutively by superscript¹ or ¹⁻³. References cited only in tables or figures should be numbered in sequence.